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STATE OF MICHIGAN
DEPARTMENT OF LICENSING AND REGULATORY AFFAIRS
BUREAU OF HEALTH CARE SERVICES
MICHIGAN MEDICAL MARIHUANA REVIEW PANEL

Dear, Director of LARA and the Michigan Medical Marihuana Review Panel,

It is with great importance that Four Freedoms submits the enclosed three packets of evidentiary documentation in response to the decision of the Michigan Medical Marijuana Review Panel to deny PTSd as a qualifying condition to the Michigan Medical Marijuana Act of 2008.

With respect to the process and individual members of the Michigan Medical Marijuana Review Panel, understanding panel's decision was based on a lack of scientific evidence and insufficient antidotal evidence.

Respectfully request the following three packages of information be presented to the Michigan Medical Marijuana Review Panel, in support of the recommendation to include PTSd in the MMMA of 2008.

Packet 1) 13 research papers supporting the use of cannabis to treat symptoms of PTSd.

Packet 2) 7 research papers supporting the use of cannabis as harm reduction.

Packet 3) New Mexico Medical Cannabis Program Advisory Board final report 7 Nov 2012, media reports relevant to issue from New Mexico, and additional antidotal evidence.

I am extremely grateful for the open and honest dialogue among the members of the panel. As a Veteran, all I can ask is that this issue be taken seriously, it is obvious from comments made by the MMMRP members, December 14, 2012 that members of the panel are focused on patient care and for that I am eternally grateful.

Additional information provided with the assistance of the following groups, Veterans for Medical Marijuana Access, The Drug Policy Alliance and Patients Out of Time.

Sincerely yours,

John Evans

Four Freedoms

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Packet #2, Research papers supporting use of cannabis as harm reduction.

Cannabis is complementary to opioid medicine for pain. Used in combination with opioids the addition of cannabis often allows a patient to decrease amount of opioid medication needed to mitigate pain, thus decreasing the potential for opioid overdose and cross prescription complication. There is wide-spread off-label use of atypical antipsychotic drugs, including that for PTSD. Use of these drugs have significant and potentially life threatening side effects.

Scan for Author Video Interview

Association of Mental Health Disorders With Prescription Opioids and High-Risk Opioid Use in US Veterans of Iraq and Afghanistan

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Context Record numbers of Iraq and Afghanistan veterans survive their war injuries and yet continue to experience pain and mental health problems, particularly posttraumatic stress disorder (PTSD). Little is known about the association of mental health disorders and prescription opioid use.

Objective To investigate the effect of mental health disorders, particularly PTSD, on risks and adverse clinical outcomes associated with prescription opioid use.

Design Retrospective cohort study involving 141 029 Iraq and Afghanistan veterans who received at least 1 non–cancer-related pain diagnosis within 1 year of entering the Department of Veterans Affairs (VA) health care system from October 1, 2005, through December 31, 2010.

Main Outcome Measures Independent association of mental health disorders and the prescription of opioids, higher risk opioid use, and adverse clinical outcomes (eg, accidents and overdose) within 1 year of receiving a pain-related diagnosis.

Results A total of 15 676 veterans were prescribed opioids within 1 year of their initial pain diagnosis. Compared with 6.5% of veterans without mental health disorders, 17.8% (adjusted relative risk [RR], 2.58; 95% CI, 2.49-2.67) of veterans with PTSD and 11.7% (adjusted RR, 1.74; 95% CI, 1.67-1.82) with other mental health diagnoses but without PTSD were significantly more likely to receive opioids for pain diagnoses. Of those who were prescribed pain medication, veterans with PTSD were more likely than those without mental health disorders to receive higher-dose opioids (22.7% vs 15.9%, adjusted RR, 1.42; 95% CI, 1.31-1.54), receive 2 or more opioids concurrently (19.8% vs 10.7%, adjusted RR, 1.87; 95% CI, 1.70-2.06), receive sedative hypnotics concurrently (40.7% vs 7.6%, adjusted RR, 5.46; 95% CI, 4.91-6.07), or obtain early opioid refills (33.8% vs 20.4%; adjusted RR, 1.64; 95% CI, 1.53-1.75). Receiving prescription opioids (vs not) was associated with an increased risk of adverse clinical outcomes for all veterans (9.5% vs 4.1%; RR, 2.33; 95% CI, 2.20-2.46), which was most pronounced in veterans with PTSD.

Conclusion Among US veterans of Iraq and Afghanistan, mental health diagnoses, especially PTSD, were associated with an increased risk of receiving opioids for pain, high-risk opioid use, and adverse clinical outcomes.

JAMA. 2012;307(9):940-947 www.jama.com

GREATER COMBAT EXPOSURE coupled with improvements in battlefield medicine and protective gear have resulted in large numbers of veterans of Iraq and Afghanistan surviving injuries that would have been fatal in prior wars.[1-3] Veterans are returning home with comorbid mental and physical health problems.[1,4] Posttraumatic stress disorder (PTSD) is the most prevalent mental health disorder among veterans of Operation Enduring Freedom (OEF, principally Afghanistan) and Operation Iraqi Freedom (OIF) who use Veterans Affairs (VA) health care,[5] the largest provider of health care for these veterans. Somatic complaints, especially pain, have been strongly associated with mental health disorders, particularly PTSD, in prior-era veterans,[6,7] and similarly, high rates of comorbid pain and PTSD diagnoses have been reported in veterans who have returned from Iraq and Afghanistan.[4,8-10]

Author Video Interview available at www.jama.com.

Nationwide, the prescription of opioid analgesics has nearly doubled since 1994 because of a greater recognition of the importance of treating pain.[11,12] At the same time, rates of prescription opioid misuse and overdose have increased sharply, and prescription opioids are now a leading cause of death

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in the United States.[12-14] Iraq and Afghanistan veterans with pain- and PTSD-prescribed opioids may be at particularly high risk of prescription opioid misuse given the high cooccurrence of substance use disorders among veterans with PTSD.[15,16] Despite media reports of overdose in these veterans with pain- and PTSD-prescribed opioids,[17,18] little is known about the association of mental health disorders and PTSD with patterns of prescription opioid use and clinical outcomes. We undertook this study in a national sample of Iraq and Afghanistan veterans enrolled in VA health care to investigate the effect of mental health disorders, particularly PTSD, on patterns of opioid prescription, associated risks, and adverse clinical outcomes, such as accidents and overdose.

METHODS

Study Population

This retrospective cohort was identified using the national VA's OEF/OIF roster, an accruing national database of veterans who have separated from military service and have enrolled in VA health care. Under a waiver of informed consent granted by the institutional review board of record, we identified veterans who entered VA health care from October 1, 2005, through December 31, 2008 (N = 291 205). We chose this period to minimize background shifts in opioid prescribing patterns in the VA because the joint VA–Department of Defense clinical practice guideline for the management of opioid therapy was released in 2003[19] and was not updated until May 2010. The main study population was defined as Iraq and Afghanistan veterans who received a new non–cancer-pain diagnosis within 1 year of VA entry (n = 141 029). Each veteran was followed up for 1 additional year from initial pain diagnosis to evaluate whether he/she received an opioid prescription and whether he/she experienced an adverse clinical outcome during this 1-year follow-up period. Selecting the subgroup with noncancer pain diagnoses allowed for increased precision with respect to indications for opioid prescription and temporal relationships among variables. The study end-date was December 31, 2010. The study was approved by the Committee on Human Research, University of California, San Francisco, and the San Francisco VA Medical Center.

Data Source

The VA OEF/OIF roster contains basic sociodemographic and military service information but lacks information on income, employment, education, and level of combat exposure and has only crude race/ethnicity categorization.[20] The roster data were linked to 2 other VA administrative databases: the VA National Patient Care Database to obtain information on VA clinical visits and associated clinical diagnoses and the VA decision support system to obtain detailed VA pharmacy records.

Study Variables

Dependent Variables. Through medical literature review and consensus of 2 internists and coauthors (K.H.S. and B.E.C.), we identified noncancer diagnoses, using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes, that could result in pain serious enough to warrant an opioid medication (eTable 1 available at http://www.jama.com).[14,21] We required at least 1 opioid prescription for a minimum of 20 consecutive days in the first year of pain diagnosis. To compare opioid doses across classes, we used a standard formula to calculate morphine equivalents.[22] Within 1 year of first pain diagnosis, we determined the following: morphine equivalent dose (in quintiles), median duration of prescription opioid use, and whether 2 or more different opioids, sedative hypnotics (eg, benzodiazepines), or both were prescribed concurrently within a 30-day period. We defined *early refill* as obtaining the same opioid prescription for more than 7 days before the end of the prior prescription as a proxy of high-risk opioid behavior. Finally, using *ICD-9-CM* diagnostic codes, we created the following categories of adverse clinical outcomes: (1) accidents resulting in wounds or injuries, (2) opioid-related accidents and overdose, (3) alcohol- and nonopioid drug–related accidents and overdose, (4) self-inflicted injuries (eg, suicide attempt), and (5) violence-related injuries (eg, gunshot wounds) (eTable 2). To ensure the clinical relevance of these outcomes, we required that outcomes occur within 1 year of pain diagnosis in the context of an emergency or inpatient admission and excluded diagnoses received as part of routine, scheduled care.

Independent Variables. We defined 3 mental health diagnostic categories: (1) no mental health diagnoses, (2) other mental health diagnoses excluding PTSD, and (3) PTSD diagnoses with and without other mental health diagnoses. Because the vast majority of individuals with PTSD have comorbid mental health disorders,[23] we did not create a separate category of those with PTSD alone. Categories were created using *ICD-9-CM* codes[20] corresponding to *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)* classifications.[24] We examined other common military service–related mental health diagnoses[20]: depressive disorders, anxiety disorders, alcohol use disorders, drug use disorders, and traumatic brain injury. Each of these conditions was examined with and without comorbid PTSD. Mental health diagnoses were included that were assigned after entry in VA health care until 1 year after receiving an index pain diagnosis. To adjust for potential confounding, we included sociodemographic (ie, age, sex, race/ethnicity, marital status, VA facility type—medical center vs community clinic) and military service characteristics (ie, component, rank, service branch, and number of deployments).[21]

Statistical Analyses

For the main study population of 141 029 veterans receiving pain-related diagnoses followed up for 1 year,

Table 1. Sociodemographic and Military Service Characteristics of Iraq and Afghanistan War Veterans With an Index Pain Diagnosis (n = 141 029)

Characteristics	No. (%) of Veterans
Age, y	
<30	81 372 (57.7)
≥30	59 657 (42.3)
Sex[a]	
Women	16 225 (11.5)
Men	124 803 (88.5)
Race/ethnicity	
White	71 384 (50.6)
Black	14 626 (10.4)
Hispanic	15 095 (10.7)
Other	39 924 (28.3)
Marital status	
Never married	72 018 (51.1)
Married	62 454 (44.3)
Divorced, widowed, or other	6557 (4.6)
Component	
National Guard or Reserve	62 315 (44.2)
Active duty	78 714 (55.8)
Rank	
Officer	9435 (6.7)
Enlisted	131 594 (93.3)
Branch	
Army	90 640 (64.3)
Marines	21 434 (15.2)
Navy	16 557 (11.7)
Air Force	12 398 (8.8)
Multiple deployment(s)[a]	
No	87 309 (62.0)
Yes	53 622 (38.0)
Primary VA facility type	
VA community clinic	40 124 (28.5)
VA medical center	100 905 (71.5)

Abbreviation: VA, Veterans Affairs.
[a]Data missing.

we used Poisson regression with robust error variance to calculate adjusted relative risks (RRs) with 95% confidence intervals. We assessed the independent association of mental health diagnostic category (no mental health diagnosis, mental health diagnosis excluding PTSD, and PTSD with and without other mental health diagnoses) with the prescription of at least 1 opioid after adjusting for individual characteristics. For comparison, we repeated the same analysis in the whole population of 291 205 returning veterans who entered VA health care from October 1, 2005, through December 31, 2008, and were followed up for 1 year. In the main study population of veterans with noncancer pain diagnoses (n = 141 029), we performed stratified analyses of subgroups of OEF/OIF veterans with PTSD vs no mental health diagnoses who were prescribed opioids using Mantel-Haenszel tests of homogeneity. Among veterans with pain-related diagnoses prescribed opioids (n = 15 676), we determined independent associations of mental health diagnostic category with prescription opioid-use patterns. Finally, we determined the prevalence of adverse clinical outcomes (defined above) for veterans within each mental health diagnostic category who were and were not prescribed opioids for pain. Because of the extremely large data set, we chose a P value of $<.001$ as a more conservative threshold for statistical significance. All analyses were conducted using SAS software version 9.1 (SAS Institute Inc).

RESULTS

Of 291 205 veterans who entered VA health care from 2005 through 2008, during 1 year of follow-up, 141 029 (48%) received at least 1 pain-related diagnosis. Sociodemographic and military service characteristics of the 141 029 veterans with an index pain diagnosis are presented in TABLE 1. The majority (66%) had received 2 or more different pain diagnoses; 51% received at least 1 mental health diagnosis—19% received mental health diagnoses excluding PTSD and 32% received PTSD diagnoses with or without other mental health diagnoses.

Opioid Prescriptions

Of the 141 029 veterans with pain diagnoses, 15 676 (11.1%) received prescription opioids for 20 or more consecutive days; 77% of which were prescribed by VA primary care clinicians. Compared with 6.5% of veterans without a mental health diagnosis, 17.8% (adjusted RR, 2.58; 95% CI, 2.49-2.67) with PTSD and 11.7% (adjusted RR, 1.74; 95% CI, 1.67-1.82) with mental health diagnoses but not PTSD were significantly more likely to receive opioids for pain (TABLE 2). Similarly, in the whole population of 291 205 veterans with and without pain diagnoses, 12.3% with PTSD (adjusted RR, 4.32; 95% CI, 4.17-4.49) and 7.3% with mental health diagnoses excluding PTSD (adjusted RR, 2.65; 95% CI, 2.54-2.77) were independently more likely to receive opioids than the 2.7% of veterans without mental health diagnoses who received opioids for pain (Table 2). In both cases, the nonoverlapping confidence intervals indicated that veterans with PTSD diagnoses were significantly more likely to be prescribed opioids than veterans with mental health diagnoses other than PTSD.

Stratified analyses confirmed that all subgroups of veterans with PTSD were significantly more likely to receive prescription opioids than those with no mental health diagnoses (FIGURE). For most subgroups assessed, the confidence intervals around the RRs of being prescribed opioids for veterans with PTSD (vs those with no mental health diagnoses) overlapped with the summary estimate. There was no significant interaction by sex, race/ethnic group, or military rank. There was significant interaction slightly diminishing the effect for veterans younger than 30 years, of active duty service, or former Marines, yet the relationship between PTSD and opioid prescription remained significant (Figure).

Veterans with other specific mental disorder diagnoses—depression, anxiety, alcohol use disorders, drug use disorders, and traumatic brain injury—were significantly more likely to receive opioids than veterans with no mental health diagnoses (eTable 3 available at http://www.jama.com). Of note, veterans with a drug use disorder and comorbid PTSD were most likely to be prescribed opioids than veterans with no mental health disorders (33.5% vs 6.5%; adjusted RR, 4.19; 95% CI, 3.84-4.57; eTable 3). Within each mental disorder diagnosis subgroup, veterans having comorbid PTSD were significantly associated with being at greater risk of receiving prescription opioids than vet-

erans with these diagnoses without comorbid PTSD (TABLE 3).

Higher-Risk Opioid Use

In the 15 676 veterans prescribed opioids within 1 year of initial pain diagnoses, we detected patterns of higher-risk opioid use in veterans with mental health diagnoses other than PTSD, but especially in veterans with PTSD (TABLE 4). Compared to veterans without mental health diagnoses, those with PTSD prescribed opioids were significantly more likely to be in the highest quintile for dose (22.7% vs 15.9%; adjusted RR, 1.42; 95% CI, 1.31-1.54), receive more than 1 type of opioid concurrently (19.8% vs 10.7%; adjusted RR, 1.87; 95% CI, 1.70-2.06), receive concurrent sedative hypnotics (40.7% vs 7.6%; adjusted RR, 5.46; 95% CI, 4.91-6.07), and obtain early opioid refills (33.8% vs 20.4%; adjusted RR, 1.64; 95% CI, 1.53-1.75). Those with PTSD compared with those with mental health diagnoses other than PTSD were significantly more likely to be prescribed opioids longer than the median duration (2 months) and to receive opioids and sedative hypnotics concurrently (Table 4).

Adverse Clinical Outcomes

Among the 141 029 veterans followed up for 1 year after receiving a pain-related diagnoses, those prescribed opioids (vs not) across all mental health categories had a higher prevalence of all adverse clinical outcomes occurring in the context of emergency department or inpatient admissions (accidents resulting in wounds or injuries; opioid-related accidents; and overdoses, alcohol- and non-opioid drug–related accidents and overdose; self-inflicted injuries; and violence-related injuries) (9.5% vs 4.1%, RR, 2.33; 95% CI, 2.20-2.46). Among veterans prescribed opioids, the absolute risk of all adverse clinical outcomes, except for wounds and injuries, was greatest for the PTSD group than for veterans without a mental health diagnosis or mental health diagnoses other than PTSD (TABLE 5).

COMMENT

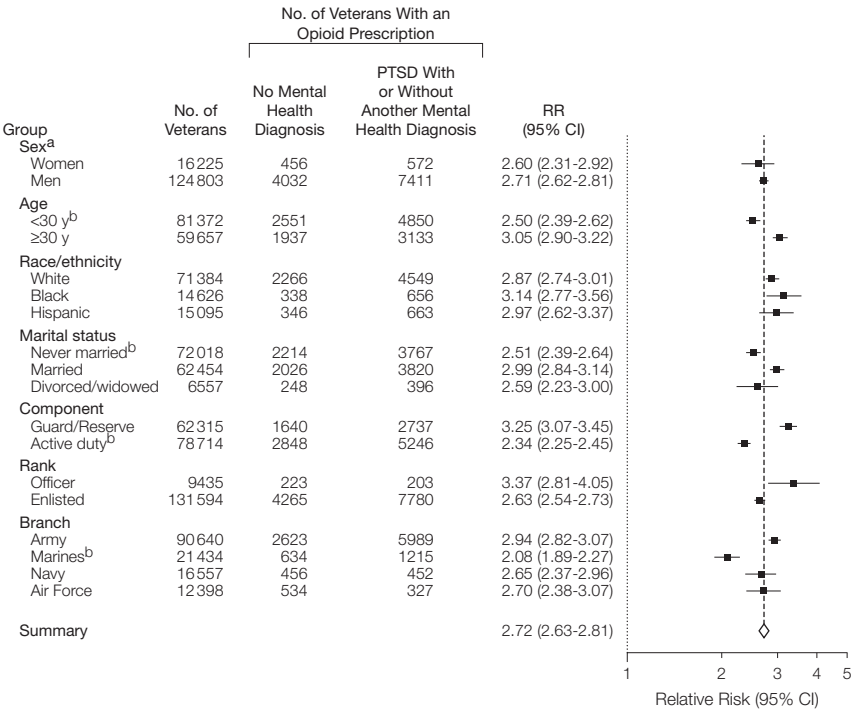
This is the first national-level study to demonstrate that veterans of Iraq and Afghanistan with mental health diagnoses, particularly PTSD, are significantly more likely than veterans with no mental health diagnoses to receive prescription opioid medications for

Table 2. Mental Health Diagnostic Category and Receipt of Prescription Opioids[a]

	Mental Health Diagnostic Category		
	None	Diagnosis Without PTSD	PTSD With and Without Another Mental Health Diagnosis
First year of pain diagnosis			
No. of veterans	68 737	27 309	44 983
No. (%) of opioid prescriptions	4488 (6.5)	3205 (11.7)	7983 (17.8)
RR (95% CI)	1 [Reference]	1.80 (1.72-1.88)	2.72 (2.63-2.81)
Adjusted RR (95%) CI[b]	1 [Reference]	1.74 (1.67-1.82)	2.58 (2.49-2.67)
First year in the VA health care system			
No. of veterans	187 452	43 656	60 097
Opioid prescriptions, No. (%)	4972 (2.7)	3176 (7.3)	7414 (12.3)
RR (95% CI)	1 [Reference]	2.74 (2.63-2.86)	4.65 (4.49-4.82)
Adjusted RR (95%) CI[b]	1 [Reference]	2.65 (2.54-2.77)	4.32 (4.17-4.49)

Abbreviations: PTSD, posttraumatic stress disorder; RR, relative risk; VA, Veterans Affairs.
[a] All *P* values are <.001
[b] Adjusted for age, sex, race, marital status, component, rank, branch of service, multiple deployments (y/n), and primary VA facility type.

Figure. Stratified Analyses of Risk of Receiving an Opioid Prescription for a Minimum of 20 Consecutive Days in the First Year of Pain Diagnosis for Veterans With a PTSD Diagnosis vs Those Without Any Mental Health Diagnosis



Although significant for all subgroups, tests for interaction showed that the effect was slightly diminished in veterans who were younger than 30 years, were never married, had enlisted in active-duty service, and were former Marines because these confidence intervals did not overlap with the summary estimate, represented as the diamond with the width representing the bounds of the summary confidence interval.
[a] Data missing.
[b] Significant differences between subgroups existed.

Table 3. Comorbid Posttraumatic Stress Disorder Diagnosis With the Receipt of Prescription Opioids by Specific Mental Health Diagnoses

Mental Health Diagnoses With and Without PTSD Diagnoses	Total No. of Veterans With a Mental Health Diagnosis	Opioid Prescription, No. (%)	Adjusted RR (95% CI)[a]	*P* Value
Depression				
Without	11 351	1541 (13.6)	1 [Reference]	<.001
With	22 616	4658 (20.6)	1.52 (1.44-1.60)	
Anxiety				
Without	7817	1012 (13.0)	1 [Reference]	<.001
With	12 158	2449 (20.1)	1.55 (1.45-1.66)	
Alcohol use disorder				
Without	3383	352 (10.4)	1 [Reference]	<.001
With	6469	1034 (16.0)	1.57 (1.40-1.76)	
Nonalcohol drug use disorder				
Without	653	167 (25.6)	1 [Reference]	<.001
With	1249	418 (33.5)	1.32 (1.13-1.54)	
Traumatic brain injury				
Without	3074	386 (12.6)	1 [Reference]	<.001
With	7461	1656 (22.2)	1.71 (1.54-1.89)	

Abbreviations: PTSD, posttraumatic stress disorder; RR, relative risk;
[a] Adjusted for age, sex, race/ethnicity, marital status, component, rank, branch of service, multiple deployments (yes/no), and primary Veterans Affairs facility type.

pain-related conditions. The association between PTSD and opioid prescription was robust because it was significant for all subgroups of veterans with PTSD. Moreover, veterans with other mental disorders (eg, substance use disorders and traumatic brain injury) were more likely to receive prescription opioids when PTSD was present as a comorbid diagnosis. Veterans with mental health diagnoses prescribed opioids, especially those with PTSD, were more likely to have comorbid drug and alcohol use disorders; receive higher-dose opioid regimens; continue taking opioids longer; receive concurrent prescriptions for opioids, sedative hypnotics, or both; and obtain early opioid refills. Finally, receiving prescription opioids was associated with increased risk of adverse clinical outcomes for all veterans returning from Iraq and Afghanistan, especially for veterans with PTSD, who were at highest risk of alcohol-, drug-, and opioid-related accidents and overdose, as well as self-inflicted injuries.

A few previous studies have reported a relationship between prescription opioid use and mental health diagnoses.[25-27] To our knowledge, only 2 prior studies have focused specifically on the use of analgesic pain medication in outpatients with PTSD.[28,29] Both studies found higher rates of prescription opioid use in patients with PTSD, particularly those with the highest PTSD symptom severity scores.[28,29] Patients with PTSD have been observed to have dysregulation of the endogenous opioid system through lower pain thresholds and lower endogenous opioid levels.[30] Unfortunately, treatment with opioids among patients with mental health problems may result in or exacerbate substance abuse and worsening of mental health symptoms over time.[25,31,32] Our results revealed that veterans with PTSD-prescribed opioids for pain used higher doses for longer periods and experienced substantially more adverse clinical outcomes than veterans with other or no mental health disorders.

Veterans with mental health problems, particularly PTSD, have barriers to seeking mental health treatment[33] and preferentially use VA primary care.[34,35] As in the broader community, most VA primary care clinicians lack specialized training in the management of comorbid pain and PTSD.[11] In a recent small study that reported an increase in chronic opioid use in younger combat veterans, 80% of opioids were prescribed in primary care settings,[36] consistent with our finding that 77% of opioids were prescribed by VA primary care clinicians. It is possible that in the primary care setting, opioids may be prescribed to treat a poorly differentiated state of mental and physical pain.[25] Morasco et al[27] demonstrated that in a sample of veterans with multiple pain problems, those with the highest-risk medical and psychiatric comorbidity were the most likely to receive the highest-dose, highest-risk opioid therapy. This paradoxical finding suggests that patient distress can drive potentially inappropriate opioid therapy, perhaps because physicians do not know how else to handle these challenging patients.[37]

Compared with other Iraq and Afghanistan war veterans, those with PTSD exhibited higher-risk opioid use and adverse clinical outcomes, including injuries and overdose. The prescription of opioids for patients who already abuse or are dependent on drugs and alcohol not only increases risk for abuse of opioids but also increases the risk of central nervous system depression and overdose.[14,38] Despite VA guidelines that urge caution in opioid prescribing for persons with substance use disorders, we found that veterans with drug and alcohol use disorders were more likely to be prescribed opioids than veterans with no mental health diagnoses; this was especially true if they also had a comorbid PTSD diagnosis.[14,38] In addition, veterans with PTSD had the greatest risk of being prescribed more than 1 opioid simultaneously and sedative hypnotic medication (typically a benzodiazepine) concurrently with opioids. The prescription of benzodiazepines is common in patients with PTSD, despite a lack of evidence for their efficacy.[39] Numerous studies have highlighted the risk of overdose from the coprescription of benzodiazepines and opioids; therefore, alternative therapies should be considered for patients with pain and PTSD.[40,41]

Some limitations must be considered when interpreting the results of this study. Data were obtained from

Table 4. Mental Health Diagnostic Category and Opioid Use Patterns Among Veterans Who Received at Least 1 Opioid Prescription Within a Year of an Index Pain Diagnosis

	Mental Health Diagnostic Category					
	None (n = 4488)		Diagnosis Without PTSD (n = 3205)		PTSD With or Without Another Mental Health Diagnosis (n = 7983)	
Proportion of Veterans With the Following Characteristics	No. (%) of Veterans	Reference	No. (%) of Veterans	Adjusted RR (95% CI)[a]	No. (%) of Veterans	Adjusted RR (95% CI)[a]
Highest quintile of average daily opioid use (≥33 mg/d)	712 (15.9)	1 [Reference]	615 (19.2)	1.22 (1.10-.34)	1813 (22.7)	1.42 (1.31-1.54)
Duration of opioid use ≥2 mo, median	1916 (42.7)	1 [Reference]	1828 (57.0)	1.33 (1.27-1.39)	5047 (63.2)	1.47 (1.42-1.53)
Concurrent opioids (>7 d overlap)	478 (10.7)	1 [Reference]	553 (17.3)	1.62 (1.44-1.81)	1581 (19.8)	1.87 (1.70-2.06)
Concurrent sedative hypnotics	343 (7.6)	1 [Reference]	802 (25.0)	3.23 (2.87-3.63)	3251 (40.7)	5.46 (4.91-6.07)
Early opioid refills	914 (20.4)	1 [Reference]	980 (30.6)	1.50 (1.39-1.62)	2701 (33.8)	1.64 (1.53-1.75)

Abbreviations: PTSD, posttraumatic stress disorder; RR, relative risk.
[a] Adjusted for sociodemographic and military service characteristics. All were statistically significant ($P < .001$) compared with those who did not have a mental health diagnosis.

Table 5. Proportion of Veterans With Adverse Clinical Outcomes by Opioid Use and Mental Health Diagnostic Categories

	Mental Health Diagnostic Category								
	None			Without PTSD			PTSD With or Without Another Mental Diagnosis		
	Opioid Use, %			Opioid Use, %			Opioid Use, %		
Adverse Clinical Outcomes	No (n = 64 249)	Yes (n = 4488)	*P* Value	No (n = 24 104)	Yes (n = 3205)	*P* Value	No (n = 37 000)	Yes (n = 7983)	*P* Value
Wounds or injuries	3.06	7.31	<.001	2.75	6.18	<.001	3.17	7.04	<.001
Opioid-related accidents and overdoses	0.01	0.02	.33	0.02	0.19	<.001	0.05	0.36	<.001
Alcohol- and nonopioid drug-related accidents and overdose	0.005	0.02	.24	0.46	0.81	.10	1.32	2.25	<.001
Self-inflicted injuries	0.01	0.02	.33	0.52	1.03	<.001	2.06	3.24	<.001
Violence-related injuries	0.15	0.36	.001	0.21	0.53	<.001	0.36	0.76	<.001

VA administrative databases that were subject to clerical errors and lacked variables such as socioeconomic status, so our results may have been subject to misclassification and residual confounding. Second, for our main analyses, we selected a population of VA-enrolled returning veterans with pain diagnoses; thus, those results cannot be generalized to all OEF/OIF veterans. When we examined the whole population of these veterans with and without pain diagnoses in VA health care system during the same period, we found that the magnitude of the risk estimates for opioid prescriptions were greater than in our original analyses of veterans with pain diagnoses. This likely occurred because when using the whole population, those with pain diagnoses (who are more likely to receive opioids) were clustered in the PTSD and other mental health diagnostic categories; whereas veterans without pain diagnoses were clustered in the no mental health diagnosis category. This clustering is expected because PTSD is strongly associated with pain and other physical symptoms.[42,43] Additionally, veterans with mental health conditions may be more likely to receive pain diagnoses because they have more clinic visits and may appear more distressed about symptoms than veterans without mental health diagnoses.[34] We mitigated these potential ascertainment biases by focusing our primary analyses on veterans who had received non–cancer-pain diagnoses.

The index pain diagnosis served as a temporal anchor after which veterans were followed up for an additional year to determine opioid prescriptions and adverse clinical outcomes, thus increasing the precision of our analyses. Nevertheless, our results represent associations between independent and dependent variables and are not evidence of cause and effect. For example, we could not verify patient adherence to opioid prescriptions because pharmacy information was derived from administrative databases. Therefore, we could not be certain that adverse outcomes occurred at the same time veterans were taking prescription opioids; only that the adverse clinical outcome occurred within the same 1-year period as opioid prescription. We could not confirm that mental health disorders, such as PTSD, increased risk for pain and opioid use or misuse because we ascertained mental health diagnoses before

and after pain diagnoses and opioid prescriptions. We chose this study design because the natural history of postdeployment mental health diagnoses is characterized by delayed onset of symptoms[44,45] and delayed detection of mental health diagnoses due to patient- and system-level barriers.[33,46,47]

Considering these limitations, our results demonstrate increased opioid prescriptions, higher-risk opioid use patterns, and increased adverse clinical outcomes associated with opioid use in veterans with pain and mental health diagnoses, particularly PTSD. These findings support further efforts to improve care of patients with comorbid pain and PTSD because of the heightened risk of self-medication with opioids and substance abuse in veterans with PTSD, which may result in further declines in interpersonal and occupational functioning.[15,25] Trials assessing the efficacy of opioids in treating chronic noncancer pain have shown only modest or equivocal benefit.[48,49] In contrast, multiple studies have described numerous harms, including overdose death, from the upsurge of opioid prescribing in recent years.[12,49]

Returning combat veterans are presenting to primary care in large numbers and are seeking relief from physical and psychological pain.[35] Extra care should be taken when prescribing opioids to relieve their distress. These patients may benefit from biopsychosocial models of pain care including evidence-based nonpharmacologic therapies and nonopioid analgesics.[50-52] Integrated treatments that target both mental health disorders and pain simultaneously are effective for both problems and may decrease harms resulting from opioid therapy.[6,8]

Author Contributions: Dr Seal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Seal, Neylan, Shi, Krebs, Maguen, G. Cohen, B.E. Cohen.
Acquisition of data: Shi.
Analysis and interpretation of data: Shi, Seal, Neylan.
Drafting of the manuscript: Seal.
Critical revision of the manuscript for important intellectual content: Seal, Shi, G. Cohen, B.E. Cohen, Maguen, Krebs, Neylan.
Statistical Analysis: Shi.
Obtained funding: Seal.
Administrative, technical or administrative support: Neylan, Seal.
Study supervision: Seal.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.
Funding/Support: This work was financially supported by the Department of Veterans Affairs (VA), Health Services Research and Development (HSRD) Research Enhancement Award Program at the San Francisco VA Medical Center (Dr Seal), by VA HSRD Career Development Awards RCD 06-042 (Dr Maguen), and CD2 07-215 (Dr Krebs), and grant K23 HL 094765-01 from the National Institutes of Health, National Heart, Lung, and Blood Institute (Dr Cohen).
Role of the Sponsor: The sponsor had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript or the decision to submit.
Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.
Online-Only Material: eTables 1 through 3 and the Author Video Interview are available at http://www.jama.com.
Additional Contributions: We would like to thank Michael Shlipak, MD, MPH, University of California, San Francisco, for his editorial comments. He was not compensated for his help. We gratefully acknowledge the sacrifices of the men and women who have served our country during war.

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PLoS one

Long-Stay Psychiatric Patients: A Prospective Study Revealing Persistent Antipsychotic-Induced Movement Disorder

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Abstract

Objective: The purpose of this study was to assess the frequency of persistent drug-induced movement disorders namely, tardive dyskinesia (TD), parkinsonism, akathisia and tardive dystonia in a representative sample of long-stay patients with chronic severe mental illness.

Method: Naturalistic study of 209, mainly white, antipsychotic-treated patients, mostly diagnosed with psychotic disorder. Of this group, the same rater examined 194 patients at least two times over a 4-year period, with a mean follow-up time of 1.1 years, with validated scales for TD, parkinsonism, akathisia, and tardive dystonia.

Results: The frequencies of persistent movement disorders in the sample were 28.4% for TD, 56.2% for parkinsonism, 4.6% for akathisia and 5.7% for tardive dystonia. Two-thirds of the participants displayed at least one type of persistent movement disorder.

Conclusions: Persistent movement disorder continues to be the norm for long-stay patients with chronic mental illness and long-term antipsychotic treatment. Measures are required to remedy this situation.

Citation: Bakker PR, de Groot IW, van Os J, van Harten PN (2011) Long-Stay Psychiatric Patients: A Prospective Study Revealing Persistent Antipsychotic-Induced Movement Disorder. PLoS ONE 6(10): e25588. doi:10.1371/journal.pone.0025588

Editor: Josef Priller, Charité-Universitätsmedizin Berlin, Germany

Received March 7, 2011; **Accepted** September 8, 2011; **Published** October 3, 2011

Funding: This work was supported by grant from the Foundation, 'The Open Ankh', The Netherlands [grant number SG 21.02]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have read the journal's policy and have the following conflicts: Dr. Bakker and Dr. de Groot have declared that no competing interests exist. Dr. van Os has been an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GSK, AstraZeneca, Pfizer and Servier, companies that have an interest in the treatment of psychosis. Dr. van Harten has received financial compensation as an independent symposium speaker from Eli Lilly, BMS, Janssen-Cilag, GSK, and AstraZeneca, companies that have an interest in the treatment of psychosis. This does not alter the authors' adherence to all the PLoS ONE policies on sharing data and materials.

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Introduction

Antipsychotics remain the cornerstone of treatment in psychotic disorder. However, they may induce several side effects, one of which is movement disorder. Antipsychotic-induced movement disorder constitutes a major reason for non-compliance, resulting in an increased risk of psychotic relapse [1–3]. In addition, a meta-analysis [4] and two recent studies showed a higher mortality in patients with tardive dyskinesia (TD) [5,6].

Antipsychotic-induced movement disorders [7,8] can be divided in acute syndromes such as parkinsonism and akathisia, that occur within days or weeks after starting an antipsychotic, or after increasing the dose, and tardive syndromes, such as TD and tardive dystonia, that develop after months or years of antipsychotic treatment. In patients on long-term treatment with antipsychotics, combinations of acute and tardive syndromes may also occur.

Although second generation antipsychotics (SGAs) may be associated with a lower incidence rate of movement disorder, these medications nevertheless still carry risk [9–18]. In patients on long-term treatment with first generation antipsychotics (FGAs), the reported prevalence of antipsychotic-induced movement disorders was around 50 to 75% [19,20]. Eleven long-term studies with SGAs (except clozapine) showed a reduced risk of drug-induced movement disorder, but not their expected disappearance [21]. These studies had several limitations such as lack of equivalent dosage of haloperidol in the control arm, high drop-out rates, short study duration and unreliable measurement of movement disorder. Three large, non-commercially funded trials published in the last five years found differences in the incidence of parkinsonism and akathisia, but no clear differences in the incidence of TD in a comparison between FGAs and SGAs (CATIE, Cutlass and EUFEST trial) [1,9,15,17]. However, these studies also had methodological limitations such as a relatively short time to detect TD (around one year), high drop-out rates, and, in the Cutlass trial, many patients in the FGA group used sulpiride which has a lower incidence of movement disorder and is classified by some researchers as an SGA. A recent prospective cohort study with TD as primary outcome found no significant difference in the incidence of TD between patients taking FGAs and SGAs [22]. Leucht and colleagues [23] demonstrated that

SGAs are a heterogenous group, each agent displaying its own particular properties. Furthermore, from a global perspective, the three antipsychotic drugs listed in the most recent (Index 2011) World Health Organization Model List of Essential Medicines are FGAs, namely chlorpromazine, fluphenazine and haloperidol (http://www.who.int/medicines/en).

Populations most at risk are those that are chronically exposed to antipsychotics, particularly when residing in hospital settings, where compliance likely is high and polypharmacy is common, further increasing risk for movement disorder [24]. Although long-stay settings are not mainstream, they remain a reality for a considerable number of patients with severe and chronic mental illness [25], and can be extended to the population in supervised residences in the community, where intake of medication often is similarly supervised. One retrospective survey reported existence of an antipsychotic polypharmacy regimen in 27.5% of the discharged patients with schizophrenia, such as concurrent use of FGAs and SGAs, in a tertiary psychiatric setting [26]. Broekema and colleagues [27] reported that the combination of SGAs and FGAs and/or anticholinergics constituted common practice in several European psychiatric hospitals. Routine cross-sectional data may not be suitable for the examination of rates of movement disorder in vulnerable populations with chronic mental illness, as drug-induced movement disorders fluctuate over time and remain underdiagnosed by both psychiatrists and neurologists [28–31].

For these reasons, a systematic and prospective assessment of movement disorder in a representative population of patients with long-term exposure to antipsychotics was used to examine the hypothesis that movement disorders remain highly prevalent in vulnerable populations.

Methods

Ethics statement

The protocol was approved by the standing Institutional Review Board, 'Medisch-ethische Toetsingscommissie Instellingen Geestelijke Gezondheidszorg' (Review Board for Human Research in Psychiatry), the Netherlands [protocol number 377].

Written informed consent was obtained from each patient; consent obtained from the next of kin was neither necessary nor recommended by the Review Board for Human Research in Psychiatry.

Subjects

A 4-year prospective naturalistic study (July 2003–May 2007) was conducted in order to determine the frequency of TD, parkinsonism, akathisia and tardive dystonia in 209 patients with chronic mental illness. To this end, a cohort was drawn from a general psychiatric hospital (GGZ Centraal, Amersfoort, the Netherlands). Inclusion criteria were: minimum age of 18 years and cumulative exposure to antipsychotics for at least 1 year. Exclusion criteria were: history of neurological disorders impacting on motor function. The cohort was representative of the population of patients with the most severe chronic mental illness requiring long-stay care, given that the hospital serves an epidemiological catchment area, is the only institute providing this type of care and patients were approached using a comprehensive list of all in-patient.

Of the patients assessed at baseline (N = 207) 93.7% (n = 194) had one follow-up and 59.4% (n = 123) had two follow-up assessments. Loss to follow-up was due to patients who were difficult to trace after leaving hospital, as well as patients dying or patients refusing assessment after inclusion.

Assessment

Patients were examined by a trained psychiatrist (PRB), using a standard protocol, described by van Harten and colleagues [32]. Patients were barefooted and seated in a chair without armrests. The researcher asked detailed questions about (i) use of chewing gum or candy at the moment of assessment as well as (ill-fitting) dentures, as both may be misdiagnosed as orofacial movement disorders, and (ii) subjective akathisia. The patient performed different tasks to assess the existence of movement disorders and to provoke abnormal movements. Thus, the following positions were adopted in succession: resting arms on the lap in different positions, arms hanging aside, stretching arms, making fast alternating hand and foot movements, opening the mouth, showing the tongue, rising from chair, and walking. Additionally, posture, rigidity and balance were assessed. Tongue dyskinesia was provoked by fingertip movements, and objective akathisia by talking conversationally while the patient was standing.

Originally, in addition to the term 'acute', the term 'tardive' (delayed) was introduced to emphasize the late-onset types of movement disorders during antipsychotic use. Yet, the definition in the current study emphasizes their persistence, which is more important [8,33].

Dyskinesia [34] was defined as hyperkinetic choreiform involuntary movements which often fluctuates in severity. TD was assessed with the Abnormal Involuntary Movement Scale (AIMS) [35,36] and case definition was based on Schooler and Kane criteria [37], requiring (i) the presence of moderate dyskinesia in at least one body area or mild dyskinesia in at least two body parts, and (ii) the absence of other conditions resulting in abnormal involuntary movements.

Parkinsonism was assessed with the Unified Parkinson Disease Rating Scale (UPDRS) [38]. A case definition of parkinsonism was based on (i) 'mild' expression of rest-tremor or rigidity as both are typical of parkinsonism, and (ii) if no tremor or rigidity was rated, the cut-off point was one rating of 'moderate' or two ratings of 'mild' on items of bradykinesia and postural stability. The more stringent criteria for items of bradykinesia and postural stability were chosen as these symptoms may be part of psychiatric syndromes or sedation. Besides this definition, an additional case definition of parkinsonism was applied in accordance with the UK Brain Bank definition, using a score of 2 in the bradykinesia items of the motor UPDRS, and a score of 1 in the items rest tremor, rigidity or postural instability of the motor UPDRS.

Akathisia [8] was defined as both subjective inner feelings of restlessness and objective motor (leg) movements. A case definition of akathisia was based on a rating of at least 'mild' on the global akathisia item. Akathisia was assessed with the Barnes Akathisia Rating Scale comprising an objective and a subjective item [39].

Dystonia was defined as a syndrome of sustained muscle contraction, frequently causing twisting and repetitive movements or abnormal postures [40]. Tardive dystonia was diagnosed, following Burke's criteria [41], if one body area attracted a rating of at least 'mild' or if two or more body areas attracted a rating of 'slight' on the Fahn-Marsden scale [42]. As frequent eye-blinking (rating of 'mild' on the item 'eye') has many causes, case definition of tardive dystonia required a rating of at least 'moderate' (blepharospasm) when 'eye' was the only symptom area.

The case definition of a persistent movement disorder was based on 2 consecutive assessments over a period of minimally 3 months, and required that individuals met case definition criteria at two consecutive assessments (hereafter: persistent movement disorder).

Guided by previous literature, variables possibly affecting risk were extracted from patients' case notes including age, sex, diagnosis according to DSM-IV, ethnic group (classified as white and non-white) and duration of hospitalization. At baseline and at each follow-up assessment, current use of antipsychotic and

anticholinergic medication was collected from the hospital and outpatient pharmacy databases.

The diagnosis 'schizophrenia' hereafter refers to DSM-IV codes 295.30, 295.10, 295.20, 295.90, 295.60, 295.70, and other diagnoses of 'psychotic disorder' to 295.40, 297.1, 298.8, 298.9.

Statistical Analyses

Frequency of persistent movement disorder was calculated in patients with minimally two assessments. Chi-squared tests and nonparametric trend tests were applied to categorical data.

Antipsychotic doses were converted to defined daily dose (DDD), assigned and reviewed by researchers of the World Health Organisation Centre of Drug Statistics Methodology (WHO, *Collaborating Centre for Drugs Statistics Methodology Available at: http://www.whocc.no/atcddd/. Accessed* December 2010). DDD was chosen as it better reflects the observed multireceptor involvement of antipsychotics, unlike classic chlorpromazine (CPZ) equivalents which are based mainly on dopamine-2 receptor occupancy. In addition, DDD equivalents are updated periodically. Anticholinergic medication was modeled as a dichotomous variable (yes/no).

Results

Sample Characteristics

Of the 209 patients included, one patient developed a brain tumor, another patient died after inclusion. All patients had a history of cumulative antipsychotic intake of minimally 1 year. Attrition was 9.8%.

Most patients were white (85.0%) and had chronic mental illness requiring long-term admission. At baseline, the mean (SD) age was 47.4 (12.8) years; men 46.3 (12.8) and women 49.1 (12.7) of age. The mean (SD) age at first admission was 25.0 (8.4) years; men 23.8 (7.6) and women 26.7 (9.3) of age at first admission. The total duration of admission was 22.1 (13.1) years. Diagnoses according to DSM-IV Axis I as defined above were: schizophrenia 69.6%, psychosis 5.3%, affective disorder 13.5%, other Axis I diagnosis 6.8% and no Axis I (with a Axis II) diagnosis 4.8%.

At baseline and follow-up, antipsychotics were used by 89.3–98.5% of the patients; FGA and SGA in 64.8–67.5% and 55.7–61.3%, respectively; FGA only and SGA only in 33.0–37.3% and 24.6–32.8%, respectively; 28.4% used both FGA and SGA at baseline; use of 0, 1, 2, 3 and 4 antipsychotic(s) was observed in 1.5–10.7%, 41.9–55.4%, 34.3–40.8%, 4.1–8.3% and 0.5–1.6%, respectively; total DDD equivalent antipsychotic use was 2.3–2.5.

Frequency over period of observation

Over the period of observation (mean = 1.1 years, SD = 0.64), at baseline and follow-up, the frequencies of movement disorder in the sample were 30.4–36.6% for TD, 21.7–32.5% for orofacial TD, 11.9–13.9% for limb truncal TD, 62.9–65.9% for parkinsonism, 13.8–26.3% for rest tremor, 6.6–15.0% for rigidity, 53.6–61.0% for bradykinesia, 8.8–10.4% for akathisia and 8.1–16.0% for dystonia. The frequency of persistent movement disorder in the sample was 28.4% for TD, 20.1% for orofacial TD, 7.7% for limb truncal TD, 56.2% for parkinsonism, 12.9% for rest tremor, 6.7% for rigidity, 48.5% for bradykinesia, 4.6% for akathisia and 5.7% for dystonia. Sixty-eight percent of the participants had at least one type of persistent movement disorder, 43.3% had a single type of persistent movement disorder, and 24.7% had at least 2 types of persistent movement disorder (Table 1). Using the UK Brain Bank definition, the frequencies of parkinsonism were 51.2–60.3% at baseline and follow-up, whereas the frequency of persistent parkinsonism was 53.1%.

Table 1. Period frequency[a] of persistent drug-induced movement disorders[b,c] (N = 194, men = 114, women = 80).

Movement disorder	N	%
Tardive dyskinesia	55	28.4
Orofacial TD[d]	39	20.1
Limb truncal TD	15	7.7
Parkinsonism	109	56.2
Rest tremor	25	12.9
Rigidity	13	6.7
Bradykinesia	94	48.5
Akathisia	9	4.6
Tardive dystonia	11	5.7

[a]Mean period was 1.1 year (SD 0.6).
[b]Persistent movement disorder: 2 consecutive positive assessments with an interval of at least 3 months.
[c]132 (68.0%) had at least one type of movement disorder.
[d]Tardive dyskinesia.
doi:10.1371/journal.pone.0025588.t001

Table 2 shows the frequency of persistent movement disorder, by age group defined by the tertile cut-offs of the age distribution. In the nonparametric test for trend, frequency of persistent TD, parkinsonism and tardive dystonia increased with increasing age ($p = 0.005$, $p = 0.000$ and $p = 0.06$, respectively). Frequency of persistent akathisia decreased significantly with increasing age ($p = 0.039$), such that the age group of 53 and older did not display any akathisia. Frequency of persistent parkinsonism in accordance with UK Brain Bank definition, by age group, was 32.3%, 56.9% and 70.3%, respectively ($p = 0.000$).

Frequency of persistent TD, parkinsonism, akathisia and tardive dystonia did not differ between FGA only and SGA only, both at baseline and at follow-up (p-values 0.506–0.898, 0.392–0.962, 0.184–0.576 and 0.424–0.916, respectively). Parkinsonism in accordance with UK Brain Bank definition did not differ between FGA only and SGA only, both at baseline and at follow-up (p-values 0.705–0.929).

Discussion

This study showed that persistent movement disorder remains highly prevalent in long-stay patients with chronic mental illness and long-term antipsychotic treatment. The high period frequency of 68% with at least a single drug-induced movement disorder is even more striking given the use of strict case definition criteria that had to be positive on at least two consecutive assessments. Clinical relevance of these findings is suggested not only because of the high frequency of these acute and tardive movement disorders, but also because persistence of movement disorder seems to be the rule. This implies that most patients on long-term antipsychotic treatment have persistent movement disorder which make this side effect a matter of urgent consideration.

Frequencies of TD, parkinsonism and dystonia were associated with older age, albeit the latter at trend significance only. In contrast, akathisia was negatively associated with older age, and even completely absent in the oldest age group. This observation could not be explained by dosage as a *post-hoc* analysis showed that total DDD equivalent at baseline and follow-up moments were neither strongly nor significantly associated with age ($r = -0.02$, $p = 0.76$; $r = -0.13$, $p = 0.08$; $r = -0.10$, $p = 0.27$, respectively). Furthermore, around 50% of the patients used more than one type

Table 2. Period frequency[a] of persistent drug-induced movement disorder[b] in 194 patients, by tertile age group.

	Age (years)[c]				
Movement disorder (%)	**≤40 (n = 65)**	**41–52 (n = 65)**	**≥53 (n = 64)**	**z[c]**	**p**
Tardive dyskinesia (n = 55)	15.4	32.3	37.5	2.78	0.005
Parkinsonism (n = 109)	40.0	49.2	79.7	4.52	0.000
Akathisia (n = 9)	7.7	6.2	0.0	−2.07	0.039
Tardive dystonia (n = 11)	1.5	6.2	9.4	1.92	0.055

[a]Mean period was 1.1 year (SD 0.6).
[b]Persistent movement disorder: 2 consecutive positive assessments with an interval of at least 3 months.
[c]Nonparametric test for trend across ordered groups (extension of the Wilcoxon rank-sum test).
doi:10.1371/journal.pone.0025588.t002

of antipsychotic with a DDD equivalent above 2.3. This is a considerable high antipsychotic dosage, as the DDD is the assumed average daily dose for a drug used for its core [43]. Yet, frequency of movement disorder between FGA and SGA did not differ.

We compared frequencies of parkinsonism between the UK Brain Bank definition and ours, and found similar results at baseline and follow-up; the same held for persistent parkinsonism.

Limitations

First, it may be hypothesized that the varying number of follow-up assessments (from 1 to 2) in the participants may have contributed to an unstable estimate. However, frequency of persistent movement disorders in those with 1 and 2 follow-up assessments were similar (data not shown). Second, the cohort in the current study was representative of the population of patients with the most severe chronic mental illness requiring long-stay care, the target population for this study. Thus, results cannot be extrapolated to the entire population of psychiatric patients exposed to antipsychotics, in whom rates of movement disorder may be different. Third, in the current study, the mean follow-up time seemed sufficient (1.1 years) to detect a persistent movement disorder because the patients were on long-term antipsychotic treatment, i.e., were exposed for a sufficiently long period to develop a persistent movement disorder. Although this study cannot draw firm conclusions regarding the persistence of movement disorders in the long run, most long-term follow-up studies nevertheless report high persistence rates. Fourth, the classic model of movement disorders originating from antipsychotics is challenged by a large body of literature and two meta-analyses [44,45] demonstrating higher prevalence rates of movement disorders in patients with a diagnosis of schizophrenia. These results provide a strong argument for the hypothesis that movement disorders may not exclusively result from antipsychotic treatment but also reflect a fundamental aspect of neurodevelopmental pathophysiology involving sensitization of dopaminergic nigrostriatal circuits [46–49]. There is no phenomenological difference between parkinsonism and dyskinesia related to schizophrenia versus drug-induced parkinsonism and dyskinesia. As a consequence, caution is required in interpreting the findings. Future prospective studies in populations of drug-naive patients with a first episode of psychosis before and after antipsychotic treatment are essential to make a distinction between primary (part of schizophrenia) and secondary (drug-induced) movement disorder. Even so, primary symptoms may develop in the course of schizophrenia making differentiation between primary and secondary symptoms difficult.

Although it is not possible to differentiate between primary and secondary movement disorders in long-stay patients, and the two types likely often occur in combination, distinguishing between the two types is of little consequence for treatment interventions which often consist of lowering the dosage of the antipsychotic, switching to an SGA (preferably clozapine), or adding an anticholinergic.

Strengths

First, all assessments were performed by a single person, who was trained and retrained (in order to prevent 'drift') regularly by the senior author (PNvH), an expert in the assessment and diagnosis of movement disorders. Second, a naturalistic and pragmatic design was used in a representative chronic psychiatric population, reflecting real-life clinical practice [50], and therefore yielding high external validity. Third, definition of persistent movement disorder was based on 2 consecutive assessments over a period of minimally 3 months, which is in contrast with many previous studies in which case definition was defined cross-sectionally. Persistent movement disorder may be a more valid measure, as it more specifically defines the disorder category given the continuously fluctuating nature of the phenotypes under investigation.

The prevalence of movement disorder from previous studies, as mentioned below, concur with the current study for TD, but they tend to be lower for parkinsonism, and tend to be higher for akathisia as well as for tardive dystonia. However, previous studies do not match with the current study, given the fact that these used cross-sectional measures and did not focus on the vulnerable subgroup of long-stay patients in hospital.

Tardive dyskinesia

Reported prevalence rates of TD vary from 3% to 70% with a median rate of 24%, most of the TD being mild, with higher rates in the elderly [51]. Van Harten and colleagues [32] reported a TD prevalence of 39.7%. A recent meta-analysis concluded that age was a likely, although not quite conclusive, risk factor for TD [52]. Other risk factors have been suggested, but with little meta-analytic support [52].

Parkinsonism

In the study by Modestin and colleagues [47] the prevalence of parkinsonism in 1995 and 2003/4 was 17% and 29%, respectively. Janno and colleagues [19] estimated the prevalence of parkinsonism at 23.2% and 72.7%, according to DSM-IV criteria and Simpson-Angus Scale criteria, respectively. Van Harten and colleagues [32] reported a parkinsonism prevalence of 36.1%. Older age may be a risk factors for parkinsonism [7], but other studies showed a higher risk in younger patients [53,54].

Akathisia

Modestin and colleagues [47] reported a 14% prevalence rate of akathisia that was constant over two time points. Janno and colleagues [19] reported prevalence rates of 31.3% and 27.3%, according to DSM-IV criteria and the Barnes scale, respectively. In the study by van Harten and colleagues [32] the reported prevalence of akathisia was 9.3%. In two retrospective studies in younger patients, neither age nor sex was related to tardive akathisia [55]. In another study, particularly younger patients taking higher dosage of (depot) antipsychotics were at risk of chronic akathisia [56]. In addition, prevalence of akathisia showed a decreasing trend with age [32].

Tardive dystonia

Van Harten and Kahn [40], reviewing 13 studies, calculated a mean prevalence of tardive dystonia of 5.3%. Earlier studies tended to show lower prevalence rates for tardive dystonia than later ones, probably owing to respectively higher and lower thresholds used, and to differences in rating scales. Van Harten and colleagues [32] reported a high prevalence (13.4%) of tardive dystonia; the high rate was thought to relate to the fact that the group examined was black and/or the fact that a careful standard examination with two investigators with a comprehensive rating scale was applied. Other studies reported comparably high prevelances of 11% [57] and 21.6% [58]. Tardive dystonia is evenly distributed across the age of onset range from 13 to 72 years, and tends to generalize in younger patients [8]. Patients developing dystonia in isolation tend to be younger than those with 'classical' TD [7].

Van Harten and colleagues [32] found a high prevalence of one or more types of movement disorders (73.7%). Furthermore, in the study by Janno and colleagues [19], 61.6% of the patients had at least one movement disorder according to DSM-IV criteria.

Having persistent drug-induced movement disorders seems to be the norm for long-stay patients with chronic mental illness and long-term antipsychotic treatment. We were surprised by the few notes about these side effects in the files of the patients, which has been found by others also [28–31]. The relative lack of focus on movement disorder syndromes is reflected in the very low rate of DSM-IV axis I diagnosis of these in routine clinical practice. Several reasons may be responsible for this discrepancy between clinical reality and clinical attention. First, it is not common practice to do a systematic investigation toward drug-induced movement disorders, which will limit recognition. Second, clinicians may wrongly assume that drug-induced movement disorders are almost not treatable. In fact, the interventions to prevent or treat akathisia and parkinsonism are evidence based and are quite easy to implement in clinical practice. Although suggested strategies to prevent/treat TD [59] or tardive dystonia [7] are not evidence-based, they resemble the strategies used to prevent acute movement disorders. In addition, novel treatment options are being developed, such as botulinum toxin, tetrabenazine, branched-chain amino acids, and, in very severe cases, deep brain stimulation [60–64]. Third, the introduction of the SGAs led to the expectation that drug-induced movement disorders would disappear but they only reduce the risk. Furthermore, antipsychotics are increasingly used for other indications as SGAs have strong mood stabilizing properties which will increase the absolute numbers of drug-induced movement disorders. Fourth, most patients with schizophrenia do not complain of their movement disorder [65–67]. Unawareness of movement disorder and subsequent lack of subjective complaints is a risk factor for diagnostic delay [66]. In addition, the unawareness notwithstanding, a movement disorder has a stigmatizing effect on patients and a negative effect on quality of life. Therefore, active assessment and treatment of movement disorder, similar to the current increased focus on metabolic syndrome, is of paramount importance. Owens [7] stated that movement disorder now can be seen as a quality-of-care-issue. In addition, shared care decision making and informed consent is part of antipsychotic treatment [68]. Systematic diagnosis may help physicians become more aware of movement disorders.

In conclusion, persistent movement disorder continues to be the norm for long-stay patients with chronic mental illness requiring long-term antipsychotic treatment, and therefore measures are required to remedy this situation, making it part of routine quality-control procedures. It may be considered somewhat ironic that long-stay patients with chronic mental illness pay a high price for the intensive care they receive, particularly because effects are likely mediated by the relatively high compliance with pharmacotherapy in these settings. Although long-stay settings are not present in abundance anymore, they are also not rare. In the U.S., over 200 state hospitals attend a declining but challenging patient population [69] and the findings likely can be extended to the considerably larger group of patients who live in supervised residential settings. Systemic screening for movement disorder takes little time and can be easily implemented in clinical practice. In addition, given the clear age dependency of some movement disorders, elderly patients are a group of special concern.

Acknowledgments

The authors are grateful to M. Hoornweg-van Beek (MSc), G.V. Boedijn (MSc), M. van Drie (MSc), R. Emons (MSc), A.E. Willems (MSc) for providing their assistance, and to all patients for participating in this study.

Author Contributions

Conceived and designed the experiments: PRB IWDG JVO PNVH. Performed the experiments: PRB. Analyzed the data: PRB IWDG JVO PNVH. Wrote the paper: PRB IWDG JVO PNVH.

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Published in final edited form as:
Trends Mol Med. 2011 February ; 17(2): 97–107. doi:10.1016/j.molmed.2010.10.010.

Antipsychotic drugs and obesity

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Abstract

Mechanisms underlying antipsychotic cardiometabolic adverse effects are incompletely understood. This hampers the identification of high-risk patients, low-risk antipsychotics and preventive/ameliorative treatments. Recent clinical, molecular, and genetic data suggest that i) antipsychotic-naïve samples provide the greatest power for mechanistic studies; ii) weight and metabolic effects can be discordant, pointing to overlapping and distinct mechanisms; iii) antipsychotics affect satiety and energy homeostasis signaling; iv) the specific peptides mediating these effects are unknown but likely overlap with those involved in idiopathic obesity; and v) single nucleotide polymorphisms in genes encoding known neurotransmitter receptors and metabolic proteins are promising pharmacogenomic targets for countering adverse affects. However, sophisticated molecular studies and genome-wide association studies, ideally in antipsychotic-naïve/first episode samples, are needed to further advance the field.

Keywords

Antipsychotics; Obesity; Weight Gain; Cardiometabolic; Risk Factors; Mechanisms; Satiety; Energy Homeostasis; Genetics

The problem of antipsychotic-related weight gain

Overweight and obesity have become a pandemic [1]. Patients with severe mental disorders are at even higher risk than the general population for obesity, cardiometabolic risk factors, and related morbidity and mortality [2,3]. In addition to medical consequences, obesity in the mentally ill can cause treatment nonadherence and decreased quality of life [4].

Although antipsychotic drugs are the cornerstone of treatment for many psychiatric disorders, these medications are significantly associated with weight gain, the development of obesity, and the accrual of cardiovascular risk factors [2–4]. These adverse effects of these medications are important factors in the reduced quality of life and premature death from cardiovascular disorders in patients with severe mental illnesses compared to the general population [3]. Moreover, treatments to prevent or ameliorate cardiometabolic side effects are scarce, only modestly more effective than placebo, and do not restore pretreatment body weight [5].

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Despite an increasing awareness of the clinical significance of antipsychotic-induced weight gain [3–6], recent data suggest that the magnitude of this side effect has been consistently underestimated by studies in chronically-treated adult populations. Such studies typically reveal an acute (≤12-week) body mass index (BMI) increase of less one unit (kg/m^2) for risperidone, one of the most commonly prescribed antipsychotics (Table 1 and Figure 1a). Conversely, the weight gain associated with early/first exposure to antipsychotics is far greater. The recently reported Comparison of Atypicals for First Episode (CAFE) trial in adults with first episode schizophrenia [8] (Figure 1a), demonstrated a nearly 1.5 kg/m^2 BMI increase after 12 weeks of treatment with risperidone, approximately three-times greater than in the first phase of the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) trial [7]. The CATIE trial is currently the largest randomized, double blind trial comparing four second-generation antipsychotics (SGAs, olanzapine, risperidone, quetiapine and ziprasidone, Table 1) with a first-generation antipsychotic (FGA, perphenazine, Table 1) in 1493 patients with chronic schizophrenia.

Moreover, studies of antipsychotic-induced weight gain in pediatric patients demonstrate consistently greater effect sizes than adult studies given similar methodologies (Figure 1a). Drug-naïve patients gain significantly more weight than patients exposed to antipsychotics in the past [11]. For example, drug-naïve pediatric patients were at far greater risk for risperidone–induced weight gain than pediatric patients as well as adult patients with substantial prior antipsychotic exposure [11, Figure 1a]. These data are taken from a recent study [11] reporting on the weight and metabolic effects of antipsychotics in a cohort of 272 antipsychotic drug-naïve (≤1 week prior treatment) pediatric patients beginning initial treatment with one of four SGAs (aripiprazole, olanzapine, quetiapine or risperidone, Table 1). The drug-induced weight gain was dramatic; patients gained significant weight on each of the SGAs with an overall mean weight gain of >10 pounds after only 12 weeks of treatment. The amount of weight gain was similar across the age range (adjusted for height), and was not affected by pubertal status, ethnicity or gender of the subjects. As shown in Figure 1a, the weight gain of risperidone was more than four-times greater than in the CATIE report that included pretreated adults.

In addition to weight gain and obesity, antipsychotics can also disturb glucose and lipid metabolism [3,4,7–11]. Metabolic abnormalities seems to be both mediated indirectly via weight gain, but also, at least with some antipsychotics (e.g., clozapine and olanzapine, Table 1), via direct molecular effects that do not require weight gain or that can even attenuate the effect of weight gain (e.g., aripiprazole, Table 1) [11].

Antipsychotic-induced cardiometabolic adverse effects have become a major issue in the treatment with SGAs. This is heightened by the fact that the broadened indications of SGAs (Table 1) have increased their use. The initially polarized view that cardiometabolic risks were associated with SGAs, but not FGAs has given way to the realization that both classes have heterogeneous cardiometabolic liabilities [3–5].

Despite the increased focus on cardiometabolic effects of antipsychotics, several questions require further clarification: i) What is the relative contribution of antipsychotic treatment, psychiatric illness, patient characteristics, and unhealthy lifestyle to the increased rates of obesity and cardiovascular morbidity in the severely mentally ill?; ii) are all (or most) antipsychotics associated with clinically relevant weight gain and/or glucose and lipid abnormalities?; iii) what are the mechanisms that link antipsychotics and cardiometabolic risk?; iv) what risk factors and mechanisms are modifiable and how can they best be targeted?; and v) what are the best approaches to answer these questions? In the following sections, we will address these questions.

Pathways to antipsychotic-related obesity

In general terms, antipsychotic-related weight gain and obesity result from a medication-induced or -aggravated imbalance between energy intake (type, amount and frequency of ingested calories) and energy expenditure (type, amount and frequency of activity/exercise) [12]. To date, data have been inconclusive whether antipsychotics increase weight via increased appetite and food intake, decreased activity or decreased metabolism. Owing to the importance of energy homeostasis, multiple and redundant pathways regulate behavior and metabolic processes related to food intake, satiety, resting metabolic rate, energy expenditure and, ultimately body weight [13]. Furthermore, in mentally ill patients receiving antipsychotics, illness effects, such as disorganization, agitation, apathy, anhedonia, depression, etc., and pharmacodynamic medication effects, including increased appetite, muscle stiffness, sedation, hypersomnia, etc., can add to these already complex interactions.

Moreover, despite the clinically significant weight gain observed in many studies with documented variability between specific antipsychotics (Table 1), there is consistent inter-individual variation even within treatment with the same antipsychotics. In the aforementioned, 12-week study of antipsychotic-naïve youth [11], for example, there were wide ranges of weight change, despite the fact that dosage ranges were relatively restricted and adherence to medication was monitored by plasma drug levels and parental interviews. For example, risperidone was associated with a mean weight gain of 5.3 kg in just 3 months, yet categorical weight gain outcomes varied considerably with some patients losing weight, whereas others gained 21% or more of baseline weight after 12 weeks of treatment (Figure 1b). The same heterogeneity was found for the other studied antipsychotics (i.e., aripiprazole olanzapine, and quetiapine, Table 1), albeit at different levels of severity [11].

This heterogeneity of the antipsychotic-induced weight gain results from poorly understood drug-gene-environment interactions, which result in a net change in the balance between peptides and hormones regulating food intake and energy homeostasis via orexigenic (anabolic) and anorexigenic (catabolic) processes [13]. Figure 2 summarizes moderators and mediators of antipsychotic-related weight gain. Moderators include patient demographics, treatment setting, illness characteristics, past and baseline antipsychotic and comedication treatments, and baseline diet, activity, and body composition. Mediators include antipsychotic dose, comedications, medication side effects and changes in diet and activity during antipsychotic exposure. Taken together, these factors interact and contribute to the observed antipsychotic-induced weight gain to varying degrees via incompletely understood mechanisms and pathways [12–14].

Moderators and mediators of antipsychotic-induced weight gain

Several moderators and mediators for weight gain during antipsychotic treatment have been reported, including patient factors (age, BMI, gender, etc.) illness-related factors (treatment naïve, extent of symptom reduction, etc.), and treatment variables (duration, dose and drug type) [4,14]. Moderator variables that have been replicated include young age and first episode illness status; these effects are likely related to minimal prior antipsychotic exposure and weight gain, rather than to developmental factors, as lower age *per se* does not correlate with weight gain in youth [11]. Although measures of antipsychotic intake, such as long treatment duration and strict medication adherence, consistently correlate with the degree of weight gain [4,14], dose-response relationship results have been mixed, with some studies finding a significant mediating effect of higher antipsychotic doses on weight gain, while others did not [16]. However, recent evidence in humans suggests a potential antipsychotic dose relationship with weight gain and metabolic abnormalities [11,15,16]. These data are supported by a six-month, fixed dose study of long-acting injectable olanzapine, which

assured full adherence; in this context, a clear dose response curve was observed [17]. Although associations with improvement in psychotic, depressive and manic symptoms have been observed [14], this relationship might be a secondary effect of greater treatment adherence and prolonged study participation in drug responders as compared to nonresponders [4].

Low baseline BMI and normal weight status (i.e., BMI< 25) have been frequently associated with greater antipsychotic-induced weight gain, but this might reflect regression to the mean [18] and not an underlying biological risk factor. In addition, a predisposition to overeating and lack of cognitive restraint [20] regarding food intake and appetite suppression might be coextensive with other mechanisms governing weight regulation more generally. Polypharmacotherapy has also been associated with greater weight gain than monotherapy [21,22]. However, this relationship is complicated by the range of medications that comprised polypharmacy, and interactions with illness severity, comorbidities and comedications, which might lead to weight gain.

Several moderating and mediating variables have been identified that modify antipsychotic-related cardiometabolic effects (Figure 2). However, available results are inconclusive, mostly due to methodological shortcomings, including small sample sizes; usually extensive prior antipsychotic treatment with unknown cardiometabolic effects; restricted number of assessed mediating and moderating variables; lack of antipsychotic blood levels; uncertain adherence levels, and the incomplete translation from animal models to human data.

Behavioral mechanisms

Although diet and exercise both moderate (as a baseline factor) and mediate (after change in response to treatment) antipsychotic-related weight gain (Figure 2) and they are amenable to direct study in humans, few clinical trials have comprehensively measured these components. It appears that patients exposed to most antipsychotics have greater appetites and eat more but the composition of their food is not necessarily altered on medication [14]. In addition to increased appetite, delayed or dampened satiety signaling has also been observed [14] and proposed as a mechanism for weight gain. However, owing to conflicting results, it remains unclear to what extent changes in energy resting metabolic rate or energy expenditure affect weight gain, whether these changes differ by drug, and whether these effects are mediated by sedation or extrapyramidal symptoms, such as parkinsonian side effects [23,24]. Some evidence from animal models addresses these questions. However, the data base is still slim and a comprehensive assessment of putative behavioral mechanisms concurrent with neurohormonal and neurotransmitter effects reviewed below is missing.

Neurohormonal mechanisms

Appetite, food intake and satiety signaling moderate and mediate antipsychotic-induced weight gain (Figure 2). Studies on animal models have produced important data regarding putative mechanisms of antipsychotic-induced weight gain [14], although results vary across species, strains, handling and housing conditions, and drug administration techniques. Results from animal studies have also been partly inconsistent with human clinical experience; examples of incongruence include the lack of weight gain of rats and mice with clozapine or in male rats with olanzapine, and weight loss of rats at high doses of antipsychotic drugs. The fact that relevant data in rodents did not match human data likely results from antipsychotic side effects in animals, such as sedation, and muscle stiffness that decrease activity and modify metabolism, thereby interacting with the antipsychotic effects on food intake, satiety and metabolism, especially in short-term trials [14].

Studies in humans have consistently shown that SGAs, especially those with strongest weight gain liabilities, increase levels of circulating leptin [25,26], a peptide hormone that regulates appetite and is produced by subcutaneous adipocytes. However, leptin increases that should decrease food intake occurred concurrent with weight gain, indicating that leptin increases are a consequence of rather than a cause of antipsychotic-induced weight gain, although the development of relative or absolute leptin resistance has also been reported [25]. Weight gain has been consistently associated with an increase in inflammatory markers [3,4,14], which are produced by both adipocytes and macrophages. Reports regarding the appetite-stimulating hormone, ghrelin have been mixed, likely resulting from the heterogeneity of patient populations, treatment types, and counterregulatory changes in appetite regulating peptides and hormones occurring in response to the antipsychotic-related weight gain. A careful review of the literature suggests that fasting morning ghrelin levels decrease early in the course of antipsychotic treatment and then increase after chronic exposure [26].

In addition to leptin and ghrelin, a host of peptides, hormones and receptors that have been associated with food intake and energy homeostasis are potentially involved in antipsychotic-induced weight gain [27,28]. Importantly, however, and in contrast to findings in rats [14], antipsychotics have not been demonstrated to bind receptors in the hypothalamus traditionally associated with weight regulation in humans. For example, binding of radiolabeled olanzapine or clozapine was not detected across 14 different hypothalamic receptors, including those with orexigenic (e.g. neuropeptide Y1 receptor), anorexigenic (e.g. neurotensin receptor 1), or fluid homeostatic (e.g. endothelin receptor) properties [29].

Because appetite and food intake increase with antipsychotics, antipsychotic effects on peptides and hormones involved in food intake and energy homeostasis have been suspected [14,27]. However, studies have been inconclusive, suffering from similar shortcomings as those focusing on moderators and mediators reviewed above. Additional factors include the selection of a limited number of examined peptides and hormones, lack of tight control of confounding variables, and reliance on peripheral markers that may or may not be a good proxy for levels of potentially etiologically important factors in the central nervous system or in peripheral tissues, such as intestine or liver.

Pharmacodynamic neurotransmitter receptor targets of antipsychotics

Strong binding (antagonism or partial agonism) at dopamine D2 receptors is the only mechanism common to all currently-approved antipsychotics and is (so far) a necessary component for antipsychotic efficacy [30]. However, the antipsychotics as a class are diverse in their targets, interacting with distinct receptor subtypes including the serotonin receptors, muscarinic acetylcholine receptors, histamine receptors, and noradrenaline receptors with varying degrees of affinity [31]. Consequently, much of the literature on antipsychotic-induced weight gain has compared neurotransmitter receptor profiles and the relative burden of each compound. In evaluating this literature, it is important to consider the probability that multiple, synergistic pharmacodynamic effects and interactions might produce weight gain phenotypes. Some of these effects could be common to many or all antipsychotics, whereas others could be specific to those with particular receptor affinities.

Dopamine

Despite the ubiquitous role of dopamine receptor blockade in antipsychotic action, this mechanism has been relatively understudied as a causal factor of weight gain. To some extent, this might derive from historical accident: prior to the reintroduction of clozapine and the subsequent development of SGAs, which were thought to be distinct from FGAs

because they interact with nondopamine receptors, antipsychotic-induced weight gain was not a major focus. However, weight gain is a feature of virtually all antipsychotics, including conventional antipsychotics (e.g. haloperidol) [32,33] that do not have the complex pharmacology of clozapine and olanzapine. A recent European study of first-episode patients with limited or no prior exposure to antipsychotics demonstrated clinically significant (≥7%) weight gain at the end of 12 months in more than half of subjects treated with haloperidol, and in 63% of patients treated with amisulpride (Table 1), which interacts exclusively with dopamine D2/D3 receptors [33]. Indeed, clinical studies in both first-episode and chronically treated patients have been notable for the relative similarities in mean weight gain observed across multiple SGAs (including risperidone and quetiapine) and FGAs [6,11,32,33,34]. This consistency, despite differences in the severity of weight gain [6,11,18], points to a potential common underlying mechanism, with D2 blockade as the most likely common factor.

Recent evidence supports a robust relationship between D2 activity and feeding behavior. For example, D2 agonists inhibit food intake in rodents [14], whereas risperidone and other antipsychotics increase food intake and core body temperature, while reducing locomotor activity in mice [14]. Moreover, food restriction increases D2 receptor levels in rodents [35], whereas obesity associates with lower D2 levels in the nucleus accumbens in humans [36]. A direct effect of leptin on dopamine neurons in the ventral tegmental area (VTA), which expresses the leptin receptor, has recently been established from two independent laboratories [37,38]. Direct administration of leptin to the VTA resulted in the activation of the intracellular JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway, reduced firing rate of VTA dopamine neurons compared to baseline or saline and decreased food intake compared to baseline [37]. Conversely, leptin-deficient mice showed reduced neuronal and behavioral (locomotor) responsivity to amphetamine compared to mice that had intact leptin signaling [38]. Taken together, these data suggest that D2 blockade might impact energy metabolism through alterations in reward signaling and decreased psychomotor activity.

Histamine

Several lines of evidence have implicated the histamine system in antipsychotic-induced weight gain. Histamine neurons are located in the posterior hypothalamus, project to many regions of the brain, and produce effects via several receptor subtypes, including the H1 receptor [39]. H1 receptor knockout animals demonstrate increased food intake, changes in feeding patterns, and obesity compared to wild-type controls [40]. Moreover, H1 receptor agonists might suppress food intake, whereas hypothalamic HI receptor antagonism increases food intake [41].

With respect to antipsychotics, Kim *et al.* [42] reported that SGAs activate hypothalamic AMP-kinase in mice, with clozapine and olanzapine having the greatest effects. Knockout of the H1 receptor, however, blocked these effects, suggesting that H1 receptor-linked activation of hypothalamic AMP-kinase could be critical in mediating antipsychotic-induced weight gain. Moreover, the affinity of antipsychotics for the H1 receptor correlated with the degree of weight gain associated with each drug. Similarly, Kroeze *et al.* [43] evaluated the binding of 17 FGAs and SGAs to multiple neurotransmitter receptors, including histamine H1, 5-HT_{2C} (5-hydroxytryptamine-2C) and dopamine D2, and found that binding to the histamine H1 receptor best predicted the reported weight gain liabilities of the antipsychotics in clinical studies.

Serotonin

Serotonin has been suggested to play a major role in regulating feeding behavior and satiety signaling. Serotonergic neurons project onto anorexigenic pro-opiomelanocortin (POMC) neurons in the hypothalamus, working in concert with leptin signaling to decrease food intake [44]. Because pharmacologic agonists of 5-HT_{2C} decrease feeding in animals [14], it is logical to conclude that 5-HT_{2C} antagonists, including most SGAs and low potency FGAs such as chlorpromazine [31], might increase food intake by impairing satiety. Several studies have demonstrated that rats treated with SGAs have increased food intake compared to untreated controls [14], and that olanzapine-induced weight gain can be abolished by the use of a pair-feeding paradigm, in which diet is yoked to the intake of a control animal [45]. Moreover, analysis of feeding patterns demonstrated increased meal size and duration rather than meal frequency in olanzapine-treated animals, suggesting delayed onset of satiety rather than decreased satiety signaling *per se* [14,45]. These results are consistent with the clinical observation that both clozapine and olanzapine can induce food craving and binge eating in human patients [46].

Notably, the two SGAs associated with the greatest weight gain, clozapine and olanzapine, are inverse agonists at 5-$HT_{2C.}$ The significance of this was demonstrated in a recent study by Kirk *et al.* [47], in which rats were exposed to a compound (SB 243213) that is a selective inverse agonist at the 5-HT_{2C} receptor. After five days, this agent produced significant weight gain compared to vehicle but less than that observed in olanzapine-treated animals. However, in combination with a potent dopamine D2-antagonist (haloperidol), the SB 243213 treated animals demonstrated a much larger weight gain, which was comparable to the effects of olanzapine. These results were not observed when mepyramine, a selective histamine H1 antagonist, was substituted. These data suggest that the histamine activity of olanzapine is neither necessary nor sufficient to produce weight gain, underscoring further the complex interactions underlying antipsychotic-induced weight gain.

Taken together, the available preclinical and human data indicate that no single one neurotransmitter system is responsible for antipsychotic-related weight gain. While rodent and indirect human evidence links the weight gain potential of antipsychotics to histamine H1 blockade [39–43], studies also implement other neurotransmitter systems [14,35–38,44–46]. These results are further supported by evidence of an interaction between histamine H1 and dopamine D2 blockade [47], genetic data [5,15,27,48–55], and by the fact that antipsychotics without relevant antihistaminergic activity, such as aripiprazole, amisulpride and haloperidol (Table 1), have clearly documented weight gain potential, especially in antipsychotic-naive and first episode patients [11,32,33]. Nonantihistaminergic candidates include dopamine D2 blockade [14,35–38], 5HT 2C blockade [44–47], and interactions with central or peripheral hormones and peptides involved in energy homeostasis [14,25–29].

Genetic mechanisms influencing antipsychotic-induced weight gain

The role of dopamine and serotonin modulation in antipsychotic-induced weight gain is further supported by pharmacogenetic data in humans [15,27,48–52]. In addition, genetic data have pointed towards a role of alpha-adrenergic transmission, G Protein, Leptin and leptin receptor activity, Promelanin-concentrating hormone (PMCH) and the cannabinoid receptor activity in antipsychotic-induced weight gain [5,48–50,53–55] (Table 3).

Surprisingly, dopamine-related genetic variation has not been widely studied with respect to the weight gain phenotype. Recently, however, two studies have implicated the dopamine D2 receptor (DRD2) in antipsychotic weight gain [15,51]. In one of these studies, a significant relationship was observed between a functional promoter polymorphism (*DRD2 -141C Ins/Del*), which affects transcription levels of the dopamine D2 receptor, and

antipsychotic weight gain [15]. Enhancing the power of this study, more than 75% of patients were antipsychotic-naïve, and all were first episode schizophrenia patients randomized to risperidone (n=32) or olanzapine (n=26). *DRD2 Del* carriers (i.e. individuals without any nucleotide at that position; n=29) were compared to *Ins/Ins* homozygotes (noncarriers, n=29) in a mixed model encompassing ten measurements over 16 weeks. *DRD2 Del* carriers gained substantially more weight compared to noncarriers after 6+ weeks of treatment, regardless of medication assignment. Mean weight gain in *Del* carriers at 6 weeks was ~six pounds greater than in noncarriers. At 16 weeks, genotype accounted for 15 pounds differential in weight gain. These data further support the notion that dopamine D2 blockade might be related to both antipsychotic effects and weight gain.

Perhaps the best studied genetic factor in antipsychotic–induced weight gain relates to the serotonin receptor, specifically at the promoter region single nucleotide polymorphism (SNP) 759T/C in the *HTR2C* gene. Initial findings of a significant interaction between antipsychotic-related weight gain and the 759T/C polymorphism in the *HTR2C gene* were obtained in antipsychotic-naïve Chinese patients, enhancing the power for the analyses. However, these findings have been replicated in several independent schizophrenia patient samples and across varying antipsychotic agents [52]. In a recent meta-analysis of eight studies, most of which were conducted with chronically ill patients, a greater than two-fold increase in risk for clinically significant (≥7%) weight gain was associated with the C allele at this SNP [52]. Since then, two large population-cohort studies have demonstrated that the C allele at this SNP is related to obesity in healthy individuals [56,57], indicating that acute antipsychotic administration might accelerate or accentuate behavioral and metabolic tendencies that could otherwise emerge.

Several pharmacogenetic studies have also tested the role of genes implicated in nonpsychiatric weight-related phenotypes. For example, the *GNB3* gene encodes a subunit of a heterotrimeric guanine nucleotide-binding protein (G protein), which integrates signals between receptors and effector proteins. The C825T SNP in the *GNB3* gene has been associated with essential hypertension and obesity, which is also associated with a high-activity splice variant of the *GNB3* gene. In a recent meta-analysis including five studies, the T allele of the C825T SNP was modestly (but significantly) associated with increased antipsychotic-induced weight gain [54].

Genome-wide association studies (GWAS) provide strong evidence for several genes, including *FTO*, *MC4R* and *TMEM18,* important in obesity and obesity-related phenotypes [58]. GWAS have the advantage of drawing on extremely large sample sizes (n>10,000) from the general population and examining >95% of the genome, so they provide fertile ground for developing testable hypotheses on the mechanisms of antipsychotic-induced weight gain. Only one GWAS has been published on antipsychotic-associated weight gain and related phenotypes [59]. Despite the heterogeneity of treatment conditions and patient history in this sample, several promising new leads for genes involved in the cardiometabolic adverse effect of antipsychotics were reported. This included genome-wide-significant results for a polymorphism in *MEIS2* for the increase in waist- and hip-circumference, a clinical proxy measure for intra-abdominal adiposity, in risperidone-treated patients. Intriguingly, this gene is involved in pancreatic development and function, providing a possible link between intra-abdominal adiposity and the development of diabetes [60]. Future GWAS in antipsychotic-naïve cohorts are needed to increase the power, which is necessary for signal detection and further hypothesis generation, as the testing of such a large numbers of SNPs requires a very high statistical threshold for significance.

Concluding remarks

Antipsychotics, which are frequently used for psychotic and nonpsychotic conditions, are associated with substantially increased appetite and weight gain, as well as increased risk for obesity and metabolic abnormalities. Taken together, the available data suggest that cardiometabolic pathology and risk factors in mentally ill patients result from several interactive factors, including i) the patient's genetic background; ii) the underlying illness; iii) unhealthy lifestyle behaviors; and iv) psychotropic medication effects.

Despite the importance of weight gain, obesity and metabolic abnormalities, the mechanisms underlying antipsychotic-related cardiometabolic adverse effect are still poorly characterized. This has interfered with the development of targeted and successful interventions for antipsychotic weight gain. In addition, because antipsychotics highly likely link to innate satiety, energy homeostasis and metabolic pathways, the lack of a detailed mechanistic understanding of antipsychotic-related cardiometabolic effects has also hampered a further unraveling of the mechanisms underlying the development and maintenance of idiopathic obesity. However, recent data support the view that antipsychotics affect key mechanisms that regulate appetite, satiety and energy homeostasis and involve hypothalamic serotonin $5HT_{2C}$, histamine H1 and cannabinoid receptors, dopamine and alpha-adrenergic transmission, as well as central and/or peripheral orexigenic and anorexigenic hormones and peptides and/or their receptors. Nevertheless, despite this body of work, many basic questions remain unresolved and should be addressed in future studies (Box 1).

Box 1

Outstanding questions

1. What are the relative contributions of illness, environmental and treatment related effects for weight gain and obesity associated with antipsychotics?
2. Can antipsychotic action be entirely separated from weight gain?
3. What are the reliable pretreatment and early intratreatment predictors of clinically relevant, antipsychotic-related weight gain?
4. What are the exact biological and environmental mechanisms of antipsychotic-related weight gain?
5. Can understanding mechanisms of antipsychotic-related weight gain lead to the development of novel antiobesity drugs for idiopathic obesity in nonmentally ill populations?
6. What are the most promising molecular and genetic targets for the development of preventive and ameliorative interventions for antipsychotic-induced weight gain?
7. To what degree are direct effects of antipsychotics that do not require weight gain responsible for metabolic complications?
8. What are the antipsychotic-related mechanisms that are uncoupled from weight gain that are responsible for glucose and lipid abnormalities?
9. Can understanding the mechanisms responsible for antipsychotic-related metabolic abnormalities that are unrelated to weight gain lead to the development of novel antidiabetic and/or lipid-lowering drugs for nonmedication-induced diabetes or dyslipidemia?

However, notwithstanding these unresolved questions, the potential for significant antipsychotic-related cardiometabolic effects has been established [3]; this risk differs across both FGAs and SGAs [3,6–11,32–34,61–63], and patients as well as behavioral factors are relevant [3–5]. Based on these findings, clinicians should: i) select antipsychotics with the least cardiometabolic liability whenever possible [3]; ii) council patients about, strongly encourage and proactively monitor healthy diet and exercise behaviors [4]; iii) monitor all patients treated with antipsychotics for the presence and emergence of cardiometabolic risk factors or disorders [3]; iv) be vigilant about the possibility of metabolic abnormalities in the absence of relevant weight gain or obesity; v) consider behavioral and pharmacologic interventions to mitigate antipsychotic cardiometabolic effects [4]; and vi) collaborate as part of an integrated care model with medical health care providers when cardiometabolic disorders emerge that require more complex medical interventions [3].

Future research is needed that takes advantage of the enhanced power obtained by studying antipsychotic-naïve individuals for proximal/early cardiometabolic effects. Likewise, for the study of distal/late effects, such as diabetes and cardiovascular events, sample enrichment strategies for the outcome under investigation should be used [64]. Although this strategy runs counter to the general procedures of excluding severely ill and metabolically compromised patients, focusing on such samples allows the focused and accelerated study of mechanisms of and risk factors for effects that take years to emerge. Furthermore, in addition to mechanistic proof of concept studies in highly selected samples, large pharmacoepidemiologic studies in generalizable samples are needed that have sufficient power to differentiate between different agents and to control for relevant confounding variables, such as prior treatment history, degree of weight gain, comedications, lifestyle, illness type and phase, comorbidities, cotreatments, etc.

Moreover, given the lack of conclusive evidence that current genetic candidates are actual susceptibility polymorphisms for antipsychotic-related cardiometabolic side effects, next generation, exploratory genomic approaches should be pursued. These hypothesis-generating studies will need to be followed by second-step hypothesis-testing of significant findings in enriched and in generalizable replication samples. Additionally, studies that go beyond the traditional weight gain approach need to be pursued. This includes the investigation of mechanisms involved in the reversal of antipsychotic-induced weight gain, focusing on peptide and hormonal changes as well as genetic factors affecting the variance in the observed weight loss after antipsychotic treatment discontinuation, after the switch to a lower risk medication, or after adding a weight loss intervention.

Finally, any novel leads from the study of antipsychotic-related cardiometabolic adverse effects should be translated into the field of idiopathic obesity research and vice versa. For example, medications tested in the idiopathic obesity field should prompt investigations of these agents in patients undergoing antipsychotic treatment [5]. Testing such agents in patients with antipsychotic-related obesity as well as in those with idiopathic obesity followed in the same study could further elucidate shared and unique pathways involved in the maintenance or reductions of abnormally elevated body weight and lipid and glucose metabolism. Given the importance of obesity and cardiometabolic risk factors, in general, and given the prevalence of antipsychotic use, in particular, the current lack of any decisive knowledge about mechanisms and best preventive treatment options should prompt an increase in the study of this important side effect cluster.

Acknowledgments

This work is supported in part by The Zucker Hillside Hospital/National Institute of Mental Health (NIMH) Advanced Center for Intervention and Services Research for the Study of Schizophrenia P30 MH 074543 and P30 MH090590 and Center for Intervention Development and Applied Research P50 MH080173, and by The Feinstein

Institute for Medical Research NSLIJHS General Clinical Research Center, Grant #M01 RR018535 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH). The article's content is solely the responsibility of the authors and does not necessarily represent the official view of NCRR, NIH or NIMH.

Glossary box

Allele	one of several alternative forms of a gene at a given locus
Anorexigenic	causing a decrease in food intake (catabolic)
Cardiometabolic adverse effects	weight gain, development of overweight or obesity, hypertension, lipid and glucose abnormalities, metabolic syndrome and related cardiovascular disorders
Extrapyramidal side effects	side effects related to dopamine blockade in the nigro-striatal system, including acute dystonic reactions, parkinsonism (rigidity, akinesia, tremor), akathisia and tardive dysinesia
Genome-wide association study (GWAS)	research examining the relationship between a given phenotype and genetic variation at more than 95% of the entire genome
Genotype	an individual's allelic status at a given locus
Mediators	factors that interact with the primary causal factor and increase or reduce its influence
Moderators	factors that represent an intermediary step between distal cause and the ultimate effect
Orexigenic	causing an increase in food intake (anabolic)
Phenotype	any characteristic of the individual that can be observed, such as height, weight, or diagnosis
Polymorphism	genetic variation that occurs with a frequency of 1% or more in the population
Promoter	the region of a gene that controls the initiation of mRNA production
Single nucleotide polymorphism (SNP)	a genetic variation potentially altering a single "letter" or base pair in the DNA

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Figure 1a.

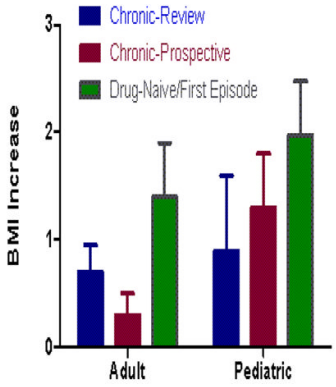

Figure 1b.

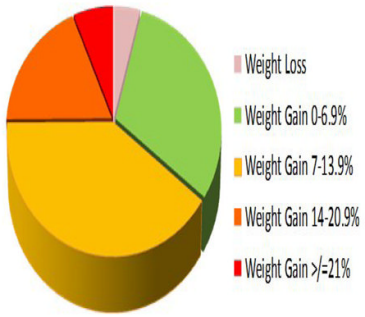

Figure 1.

Figure 1a. Effect of prior treatment exposure on BMI increase with risperidone in adults and youth [6–11]. The difference in the magnitude of weight gain associated with risperidone depends on patient age and treatment history. In adults and youth, the weight gain in antipsychotic-naïve and first-episode patients (green bar) is far greater than in patients with chronic illness and treatment exposure, either in pooled reviews (blue bars), or prospective studies (red bars). In comparison to adults, the weight gain in youth, and especially in those with no more than seven days of lifetime antipsychotic exposure (green bar on the right), was the greatest. The blue and red bars, respectively, at the left of Figure 1a display data summarized in a recent review [6], and data derived from the large-scale prospective CATIE trial [7].

Figure 1b. Heterogeneity of weight gain in antipsychotic-naïve youth treated with risperidone for three months [11]. The pie chart shows the heterogeneity of three-month weight gain in 135 children and adolescents receiving risperidone who were part of a cohort study of 272 antipsychotic-naïve youth. Despite a mean weight gain of 5.3 kg, weight gain outcomes varied considerably: weight loss occurred in 4.4%; weight gain of 0–6.9% of baseline body weight occurred in 31.1%; of 7–13.9% in 39.6%; of 14–20.9% in 18.5%; and of ≥21% in 6.7% of youth.

Figure 2.
Model of antipsychotic-induced weight gain. The heterogeneity of antipsychotic-induced weight gain results from still poorly understood drug-gene-environment interactions. Moderators of antipsychotic-induced weight gain include variables related to patient demographics, treatment setting, illness characteristics, past and baseline antipsychotic and comedication treatments, and baseline diet, activity, and body composition. Mediators include antipsychotic dose, comedications, medication side effects and changes in diet and activity. Taken together, these factors interact in specific ways leading to antipsychotic-induced weight gain via so far incompletely understood mechanisms and pathways.

Table 1

Neurotransmitter and cardiovascular risk characteristics of selected first- and second-generation antipsychotics [3–11,31–34,62,63]

Antipsychotic	Neurotransmitter targets	FDA indication	Risk level weight gain	Risk level lipid abnormalities	Risk level glucose abnormalities
FGAs (selection)					
CHLORPROMAZINE (Thorazine®)	Cholinergic M1 > serotonin 5HT2A > histamine H1 > > dopamine D2	Schizophrenia, bipolar mania (acute)	High	High	High
HALOPERIDOL (Haldol®)	Dopamine D2 > all other neurotransmitter receptors	Schizophrenia	Low	Low	Low
MOLINDONE (Moban®)	Dopamine D2 > all other neurotransmitter receptors	Schizophrenia	Low	Low	Low
PERPHENAZINE (Trilafon®)	Dopamine D2 > all other neurotransmitter receptors	Schizophrenia	Low	Low	Low
SGAs					
AMISULPRIDE (Solian®)	Dopamine D2 (putatively with regional selectivity)	Schizophrenia (not in the US)	Low	Low	Low
ARIPIPRAZOLE (Abilify®)	Partial dopamine D2 agonism (> serotonin 5HT 1a partial agonism >/= serotonin 5HT2A)	Schizophrenia (acute and maintenance, pediatric and adult), bipolar mania (acute (also as adjunct) and maintenance, pediatric and adult), unipolar depression (adjunct only)	Low	Low	Low
ASENAPINE (Saphrys®)	Serotonin 5HT2C > Serotonin 5HT2A > histamine H1 > alpha 1 >/= alpha 2 >/= dopamine D2	Schizophrenia (acute and maintenance); bipolar mania (acute)	Low	Low	Low
CLOZAPINE (Clozaril®)	Cholinergic M1 > serotonin 5HT2A> histamine H1 > serotonin 5HT2C > alpha 1 > alpha 2 ≫> dopamine D2	Schizophrenia (refractory)	High	High	High
ILOPERIDONE (Fanapt®)	Serotonin 5HT2A > alpha 1 ≫ alpha 2 >/= dopamine D2	Schizophrenia (acute)	Intermediate	Intermediate	Intermediate
OLANZAPINE (Zyprexa®)	Histamine H1 > serotonin 5HT2A> cholinergic M1 > serotonin 5HT2C > dopamine D2	Schizophrenia (acute and maintenance, pediatric and adult), bipolar mania (acute and maintenance, pediatric and adult), unipolar depression (only in combination with fluoxetine)	High	High	High
PALIPERIDONE (Invega®) [active metabolite of risperidone]	Serotonin 5HT2A >dopamine D2	Schizophrenia (acute and maintenance), schizo-affective disorder (acute)	Intermediate	Intermediate	Intermediate
QUETIAPINE (Seroquel®)	alpha 1 > histamine H1 > serotonin 5HT2A > alpha 2 > cholinergic H1≫ dopamine D2; serotonin reuptake inhibition	Schizophrenia (acute and maintenance, pediatric and adult), bipolar mania (acute and maintenance-as adjunct only, pediatric	Intermediate	High	Intermediate

Antipsychotic	Neurotransmitter targets	FDA indication	Risk level weight gain	Risk level lipid abnormalities	Risk level glucose abnormalities
		and adult), bipolar depression; unipolar depression (adjunct only)			
RISPERIDONE (Risperdal®)	Serotonin 5HT2A ≫ alpha 1 > dopamine D2	Schizophrenia (acute and maintenance, pediatric and adult), bipolar mania (acute - also as adjunct, pediatric and adult; maintenance-only as long acting injectable)	Intermediate	Intermediate	Intermediate
ZIPRASIDONE (Geodon®)	Serotonin 5HT2A ≫ dopamine D2; serotonin 5HT 1a partial agonism; noradrenaline reuptake inhibition	Schizophrenia (acute and maintenance), bipolar mania (acute and maintenance-adjunct only)	Low	Low	Low

Table 2

Appetite-regulating factors possibly involved in antipsychotic-related weight gain

Ligand	Receptor
Appetite-Stimulating (orexigenic)	
Hypothalamus-related signals	
Melanin-concentrating hormone (MCH)	MCH receptor
Orexin A/B = hypocretin I/II	Orexin A/B receptor
Neuropeptide Y (NPY)	Neuropeptide Y_1 and Neuropeptide Y_5
Agouti-related protein (AGRP)	Melanocortin 4 receptor (MC4R)
Galanin	Galanin receptor
Endocannabinoids (anandamine, 2-arachidonoyl glycerol)	Cannabinoid 1 receptor (CB1-R)
β-endorphin	μ-opiate receptor
Enkephalins, dynorphins	δ, κ-opiate receptors
Adiposity-Related Signals	
Ghrelin	Growth hormone secretagogue (GHS)
Appetite-Suppressing (anorexigenic)	
Hypothalamus-Related Signals	
Corticotropin releasing hormone	Corticotropin hormone I/II receptor
Growth hormone-releasing hormone (GRH)	GRH receptor
Thyreotropin-releasing hormone	Thyreotropin-releasing receptor
Melanocortin, melanocyte-stimulating hormone (α- MSH)	Melanocortin 4 receptor (MC4R)
Oxytocin	Oxytocin receptor
Galanin-like peptide	Galanin-like peptide receptor
Cocaine-amphetamine-regulated transcript (CART)	?
Prolactin-releasing neuropeptide	Prolactin-releasing neuropeptide receptor
Brain-derived neurotrophic factor (BDNF)	BDNF receptor
Ciliary neurotrophic factor	Ciliary neurotrophic factor receptor
Neurotensin	Neurotensin receptor
Urocortin I/II/III	Corticotropin-releasing factor receptor 1/2
Adiposity-Related Signals	
Leptin	Leptin receptor
Insulin	Insulin receptor
Tumor necrosis factor-alpha (TNF-α)	TNF receptor
Interleukin (IL) 1 and 2	IL-1 and IL-2 receptors
Meal-Related Signals*	
Cholecystokinin (CCK)	CCK A/B = I/II receptor
Bombesin	Bombesin receptor subtype 3 (BRS3)
Gastrin-releasing peptide	Gastrin-releasing peptide receptor
Glucagon	Glucagon receptor

Ligand	Receptor
Glucagon-like peptide-1 and 2 (GLP-1/2)	GLP-1/2 receptors
Oxyntomodulin	Oxyntomodulin receptor
Neuromedin B	Neuromedin B receptor
Enterostatin	Enterostatin receptor
Amylin	Amylin receptor
Apolipoprotein A-IV	Apolipoprotein A-I/AII receptors
Pancreatic polypeptide	Pancreatic polypeptide receptor
Somatostatin	Somatostatin receptor
Peptide YY3-36	Neuropeptide Y Y2 receptor

* Many "meal-related" signaling peptides and hormones are produced in the central nervous system and have nonmeal-related functions as well.

Table 3

Genetic polymorphisms associated with antipsychotic-related weight gain

Risk Gene (Chromosomal location)	Genetic mutation
Alpha-$_{2A}$Adrenergic receptor gene (10q24-26)	−1291C/G (rs1800544)
Cannabinoid receptor (CNR) 1 gene (6q14–q15)	rs806378 385C/A
Dopamine receptor D2 (DRD_2) gene (11q22–q23)	−141C Ins/Del rs4436578-C
G-Protein beta3 subunit (GNB3) gene (12p13)	C825T
Leptin gene (7q31.3)	−2548A/G (rs7799039)
Leptin receptor gene (1p31)	K109R (rs1137100) Q223R (rs12131454) K656N (rs8179183) 2548A/G
PMCH gene (12q23–q24)	rs7973796
Serotonin 2C ($5HT_{2C}$) receptor gene (Xq24)	−759C/T (rs3813929) c.1–142948(GT)n 13 repeat allele common allele rs3813929 C variant allele rs518147 C variant allele rs1414334 C

Published in final edited form as:
Pharmacoepidemiol Drug Saf. 2011 February ; 20(2): 177–184. doi:10.1002/pds.2082.

INCREASING OFF-LABEL USE OF ANTIPSYCHOTIC MEDICATIONS IN THE UNITED STATES, 1995-2008

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Abstract

Objective—To evaluate patterns of antipsychotic use.

Design, setting, and measurements—We used nationally representative data from the IMS Health National Disease and Therapeutic Index to describe outpatient antipsychotic use. The primary outcome was the volume of visits where antipsychotics were used for specific indications (treatment visits). We also quantified use without U.S. Food and Drug Administration approval (off-label use) and off-label use with compendium data suggesting an uncertain evidence base.

Results—Antipsychotic use increased from 6.2 million (M) treatment visits (95% CI, 5.4-7.0) in 1995 to 16.7M visits (15.5-18.2) in 2006, then declined to 14.3M visits (13.0-15.6) by 2008. A shift occurred from typical agents in 1995 (84% of all antipsychotic visits) to atypical agents by 2008 (93%). As they declined, typical medications shifted towards use in schizophrenia (30% in 1995 to 48% 2008). In contrast, use of atypical agents expanded for bipolar affective disorder (10% to 34%), remained stable for depression (12% to 14%), and declined for schizophrenia (56% to 23%). Overall, antipsychotic use for indications without FDA approval increased from 4.4M visits in 1995 to 9.0M in 2008. The estimated cost associated with off-label use in 2008 was US $6.0 billion.

Conclusions—Atypical use has grown far beyond substitution for the now infrequently used typical agents. Antipsychotics are increasingly used for conditions where FDA approval and associated clinical evidence is less certain. Despite the value of innovation, the benefits of widening atypical antipsychotic use should be weighed against their cost, regulatory status, and incomplete nature of available evidence.

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Disclosures
Dr. Alexander is a consultant for IMS Health.

BACKGROUND

With their availability a half-century ago, antipsychotic medications revolutionized the treatment of psychiatric disease. Over the last two-decades, first generation or "typical" agents introduced in the late 1950s and 1960s have largely been replaced by a second generation of "atypical" antipsychotics. Recently, considerable attention has focused on atypical antipsychotics due to their increasingly prevalent use and high cost (1), as well as concerns regarding their safety (2), comparative efficacy (3), and off-label use in the absence of strong evidence (4). Atypical antipsychotics accounted for more than $13 billion dollars in U.S. prescription drug costs in 2007, nearly 5% of all U.S. drug expenditures (5). Among them, quetiapine, aripiprazole, olanzapine, and risperidone, each had annual U.S. sales exceeding $1 billion (6,7).

The shift towards atypical use has been partly driven by their lower risk of extrapyramidal (motor) adverse effects compared to typicals. As long-term experience has accrued, however, serious and distinct adverse effects of atypicals have emerged. Atypical antipsychotics cause weight gain and lead to a higher risk of diabetes and other metabolic sequelae than their typical counterparts (8). Compared to nonusers, there is an increased risk of mortality and cardiovascular events in elderly patients with dementia on atypicals (9). In addition, current comparative evidence suggests no definitive differences in efficacy or net adverse effect profiles between these two drug classes (10). Although approved initially for schizophrenia, antipsychotic medications also are used for numerous other conditions, including other psychoses, bipolar disorder, delirium, depression, personality disorders, dementia, and autism (11,12). While some atypical drugs have received FDA approval for limited aspects of these conditions, the evidence base for many off-label uses remains less certain than for those drugs with regulatory approval.

We examined long-term U.S. trends in physician use and costs of antipsychotics with focus on the clinical divergence of typical and atypical medications over the past fifteen years. Using nationally representative data on office-based visits from 1995 through 2008, we tested the hypothesis that with the shift to atypical agents, costly antipsychotic use is increasingly occurring in clinical situations lacking FDA approval and where evidence is less certain.

METHODS

Data source

We used physician survey data from the IMS Health National Diagnostic and Therapeutic Index (13) (NDTI). NDTI selects a random sample of office-based, patient-care physicians through stratified sampling by specialty and geographic region. Approximately 4,800 physicians participate each calendar quarter and each physician is randomly assigned two consecutive workdays per quarter for data collection. For each encounter, physicians complete an encounter form that captures a listing of the patients' diagnoses and, for each diagnosis, a listing of associated medications that are newly prescribed or to be continued at the visit's conclusion. Although the majority of encounters take place in the outpatient office setting, the NDTI also captures phone-based encounters and those taking place in long-term care institutions (approximately 3-5% of encounters) or hospitals (approximately 10%).

Trends in antipsychotic medication use

We queried these data for patient visits where a typical or atypical antipsychotic drug was reported (referred to as a treatment visit). We report national estimates that were extrapolated from the sample data for visits by patients of all ages. For each estimate, 95% confidence intervals (CI) were available via estimates of the relative standard error.

Analyses comparing NDTI with the U.S. National Center for Health Statistics' National Ambulatory Care Medical Survey (NAMCS) suggest consistency in assessing patterns of outpatient care (14,15).

Classifying prescription use based on FDA labeling and available evidence

Based on the physician-reported diagnostic codes associated with each antipsychotic medication treatment visit, we searched the FDA website (16) to determine whether the reported indication had obtained FDA approval. We conservatively defined off-label use as lack of FDA approval through 2008, even when assessing use in earlier years. For these off-label indications, we used a widely referenced drug compendium, Drugdex® (12), to obtain summary information on the evidence base supporting each indication. We analyzed evidence at a drug, rather than class, level. We did so both because of the difficulty defining class effects for the chemically and clinically heterogeneous antipsychotics (17,18), and because the FDA approaches drug approval at the level of individual drugs. We characterized the evidence base for an off-label use as either "moderate or strong" or "uncertain." "Moderate or strong" includes only those indications where Drugdex efficacy was "effective" or "favors efficacy," the strength of evidence rating indicated RCT-derived evidence ("A" or "B"), and the strength of recommendation rating was "recommended," "recommended for most patients," or "recommended for some patients." All indications not meeting these criteria were classified as having uncertain evidence.

Prescription expenditures

We obtained information on prescription expenditures from IMS Health National Sales Perspective and the IMS National Prescription Audit. We derived information on the mean price per day of therapy, as well as aggregate annual expenditures. These costs reflect funds paid for prescriptions by both health insurance and the patient.

Role of the funding source and institutional review

The study was supported by awards from the U.S. Agency for Healthcare Research and Quality, the Robert Wood Johnson Foundation, and the National Heart, Lung and Blood Institute, while the data were obtained under licensed agreement with IMS Health. These sources of funding and data had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript for publication. The study was determined to be exempt from Institutional Review Board review at the University of Chicago.

RESULTS

Overall trends for typical and atypical use

Annual antipsychotic treatment visits nearly tripled from 6.2 million (M) treatment visits (95% confidence interval, 5.4-7.0) in 1995 to 16.7 M (15.5-18.2) in 2006, but then declined to 14.3 M (13.0-15.6) by 2008. Typical antipsychotics decreased from 5.2 M (4.5-5.9) visits in 1995 to 1.0 M (0.8-1.3) visits in 2008, while atypical antipsychotics increased from 1.0 M (0.8-1.2) to 13.3 M (12.0-14.5) visits. This shift from typical agents (84% of antipsychotics in 1995) to atypical agents (93% in 2008) occurred in two phases (Figure 1). First, from 1995 through 2001, atypical antipsychotics increased primarily as they substituted for typical agents without change in the overall volume of antipsychotic use. Second, from 2002 through 2006, atypical antipsychotic prescribing increased more substantially, with only modest further reductions in the use of typical agents. More recently, there have been declines in the use of both typical and atypical antipsychotics.

Most common antipsychotic medications

In 1995, the most commonly reported antipsychotic medications were the typical agents haloperidol (1.2 M treatment visits), thioridazine (1.0 M), and perphenazine (0.8 M). The two available atypical antipsychotics in 1995 were clozapine (0.2 M) and risperidone (0.8 M). In 2008, the most commonly reported atypical agents were quetiapine (16.7 M) risperidone (12.0 M), aripiprazole (6.7 M) and olanzapine (6.2 M). Among typical agents, haloperidol was most widely used (2.5 M, Table 1).

Relative growth among children, non-elderly adults, and the elderly

Patterns of increasing antipsychotic use varied by patient age. The largest changes occurred among adults, ages 18-64 years old. In this age group, antipsychotic use (atypical and typical) was stable between 1995 (4.1 M treatment visits, 95% confidence intervals [CI], 3.5-4.7) and 2001 (5.1 M treatment visits, CI 4.4-5.8) and then increased markedly to 11.9 (CI 10.7-13.1 M treatment visits by 2006. Similarly, the number of treatment visits among those 65 years and older were constant between 1995 (1.4 M visits, CI 1.1-1.7) and 2000 (1.3 M visits, CI 1.0-1.6) after which they increased to a maximum of 2.2 M (CI, 1.8-2.6) in 2003 with modest decline to 1.6 M, CI 1.2-2.0 by 2008. The number of treatment visits among children increased eight-fold from 1995 (0.3 M CI 0.2-0.4) to 2005 (2.4 M CI 2.0-2.8).

Changes in clinical uses of typical and atypical antipsychotics

A substantial shift occurred in the clinical uses of antipsychotics between 1995 and 2008 (Table 2). The fraction of all typical antipsychotic used for patients with schizophrenia increased from 32% of typical treatment visits in 1995 to 53% in 2007 and decreased to 48% in 2008. In contrast, for schizophrenia declined from 56% of all atypical agent treatment visits in 1995 to 23% in 2008, while there was a substantial increase in use for bipolar affective disorder (10% to 34%). Atypical antipsychotic use for depression increased from 12% of all atypical treatment visits in 1995 to 18% in 2003 and then dropped to 14% of uses by 2008. The proportion of atypical use for other disorders (e.g., dementia, anxiety disorders) was stable during this period.

Changes in Off-label Use

In 1995, 74% of all antipsychotic treatment visits (or 4.4 M visits) were for conditions that were not approved by the FDA by 2008. By 2008, 60% (or 9.0 M visits) were off-label. For atypical antipsychotics, off-label uses increased from 50% in 1995 to 66% in 2003, before declining to 60% in 2008. For typical agents, off-label use declined from 78% in 1995 to 67% in 2008.

Exploratory analyses of use by levels of evidence

Among the 4.4 M antipsychotic off label uses in 1995, 4.2 M (97%) had a compendium summary suggesting an uncertain evidence base. In 2002, among the 6.8 M off-label use visits, 5.5 M (81%) had uncertain evidence. By 2008, 8.2 M (91%) of the 9.0 M off-label visits had uncertain evidence. Among atypical agents, off-label use with uncertain evidence increased from 0.44 M visits (45% of atypical off-label use) in 1995 to 6.9 M visits (54% of atypical off-label use) in 2008. Among typical antipsychotics, 3.6 M visits (76% of typical off-label uses) in 1995 were with uncertain evidence, compared to 0.8 M visits (65% of typical off-label uses) in 2008. The majority of increases in off-label use were due to increasing use among adults younger than 65 years for indications with uncertain evidence, rather than among children or the elderly.

Antipsychotic medication costs

From 2004 to 2008, the mean cost of typical antipsychotic prescription increased 8% from $38 to $41, while the cost of an atypical prescription increased by 43% from $226 to $323. In 2008, US$0.06 billion was spent on typical agents and $9.9 billion spent on atypical agents in the United States. Given these costs, we estimate that in 2008 $6.0 billion was expended on off-label use of antipsychotic medications, of which $5.4 billion was for uses with uncertain evidence.

DISCUSSION

From 1995 to 2008, there was a pronounced shift in the use of atypical antipsychotic drugs. Based on nationally representative serial, cross-sectional data from U.S. outpatient physician practices, we found a 45% decrease in the proportion of use for schizophrenia, for which most drugs were initially labeled, and a nearly seven-fold increase in use for bipolar affective disorder, representing a third of all uses with atypical agents in 2008. Rates of atypical use for depression did not change substantially over the period examined. Significant divergence in the application of typical and atypical agents was evident, with the small residual use of typical agents concentrated in prescribing for schizophrenia.

Antipsychotic medications are one of the most common and costly classes of prescription drugs in the U.S. While their increasing use has been widely reported, far less is known regarding the evolution of their clinical uses. While others have noted the shift towards antipsychotic use for mood disorders (19,20), our report reinforces the magnitude of this shift using with national U.S. data collected over an extended observation period with clinician-reported diagnoses.

Previous studies have demonstrated a substantial replacement of typical antipsychotics with their newer counterparts following the market release of the first atypical agent in 1989. This increase has occurred despite a lack of definitive advantages of the atypical agents over their typical predecessors in their efficacy and adverse effect profiles. Recent trials (22,23) failing to demonstrate clinically significant differences in the effectiveness of these two classes in schizophrenia raise the question of whether typical antipsychotics should be reconsidered as a first line therapy, given that the superiority of atypical agents has yet to be established. Such a shift in practice, however, is unlikely given the potency of a variety of non-clinical factors that shape prescribing, including clinical inertia and the continued marketing of atypical agents. This is especially important given the small share of all antipsychotic use accounted for by typical agents, as well as the divergence in the use of typical and atypical antipsychotic medications.

Prescription drugs vary in their clinical and biochemical innovation, and in many cases important discoveries regarding therapies are made only after market release, often to treat conditions distinct from those initially targeted. The effectiveness of selective serotonin reuptake inhibitors (SSRIs) to treat anxiety, and the use of angiotensin converting enzyme-inhibitors (ACE inhibitors) in congestive heart failure, are but two examples where drugs approved for one use were subsequently found to have other important clinical applications. Although typical and atypical antipsychotics were not initially developed for use in bipolar affective disorder, subsequent evidence suggests their efficacy in treating mania associated with this disease (24). While increasing antipsychotic use since 1995 reflects clinical innovation and other factors, it has led to clinical use where regulatory scrutiny has not occurred and where the supporting evidence is less certain.

Innovation in clinical practice necessarily involves the use of therapies that are not well studied. When the application of therapies for new and largely untested clinical indications

reaches a substantial volume, however, there should be a corresponding obligation to generate evidence that demonstrates the safety and efficacy of the new uses. This is especially important in clinical settings where alternatives to the innovative therapies are already available, as with mood stabilizers (e.g., divalproex) for bipolar affective disorder and antidepressants (e.g., selective serotonin reuptake inhibitors) for the treatment of depression. Further scrutiny of widespread psychotropic medication use for scientifically unsupported off-label indications is needed, especially among those patient subpopulations and clinical applications where such uses are most common.

Our study has several important limitations. First, because the NDTI is a visit-based sample of outpatient office practices, it oversamples those with greater comorbid illness compared with population-based samples. Nevertheless, visit-based samples are commonly used for this type of analysis, and the NDTI provides data congruent with the National Ambulatory Medical Care Survey conducted by the U.S. government (14,15). Second, as with many other data sources, NDTI lacks information that would be useful in understanding the choice of off-label use, such as data regarding patient non-response to FDA approved therapies and detailed comorbid histories. Third, since there is no single source that includes summary information on drug safety and effectiveness, drug compendia vary in their assessments of the levels of evidence supporting different clinical applications (25). Despite its limitations, Drugdex® serves as a key source of information that is updated regularly, commonly used in clinical practice, and recognized in U.S. reimbursement regulations, including Medicaid evaluation of coverage for off-label uses (26). As with any method of determining levels of evidence, our estimates are subject to imprecision due to these limitations of drug compendium data and NDTI's sparse clinical detail. Even if significant misclassification were to have occurred, however, our results would still suggest a substantial exposure to therapies for clinical indications that have not received regulatory scrutiny and where the evidence base is uncertain. If only 30% of all atypical uses in 2008 were to have uncertain evidence (a conservative estimate compared with our derived estimate of 54%), this would translate into an estimated 3.8 M prescriptions at a cost of $3.0 billion.

Antipsychotic medications have important known benefits and risks. Our data suggest substantial growth of atypical antipsychotics beyond their substitution for older, typical antipsychotics. Patterns of clinical use have diverged for typical and atypical agents. The use of typical agents has declined, but continues predominantly for schizophrenia. In contrast, atypical agent use has dramatically increased, both substituting for typical agents and expanding into new indications, such as bipolar disorder and depression. Despite the value of innovation, expansion of clinical practice beyond FDA approved indications raises significant concerns. Further expansion of atypical antipsychotics should be approached with caution while awaiting new evidence evaluating their comparative benefits. This information is important not only for non-elderly adults who comprise the majority of atypical use, but also for children and the elderly, vulnerable populations where increasing rates of atypical use are also noted.

Acknowledgments

The authors gratefully acknowledge analytic assistance from Shu Zhu, MPH, in preparing the manuscript. The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (1995-2008); Integrated Promotional Services™ (2001-2008), National Prescription Audit™ (2001-2008), IMS Health Incorporated. All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

Funding

Dr. Alexander has career development awards from the Agency for Healthcare Research and Quality (K08 HS15699; RO1 HS0189960) and the Robert Wood Johnson Physician Faculty Scholars Program. Dr. Stafford has a mid-career development award from the National Heart, Lung and Blood Institute (K24 HL086703). The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; and preparation, review, or approval of the manuscript for publication.

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APPENDIX FIGURE 1.
ASSESSMENT OF SCIENTIFIC SUPPORT FOR EACH DRUG-USE COMBINATION.

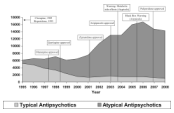

FIGURE 2.
AGGREGATE USE OF TYPICAL AND ATYPICAL ANTIPSYCHOTICS, 1995-2008.*
*Source: IMS Health National Disease and Therapeutic Index™, 1995-2008

Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2012 February 1.

TABLE 1

ANTIPSYCHOTIC MEDICATIONS BY TREATMENT SUBCLASS.*

	Total prescriptions 2008 (M)	95% confidence intervals (M)	Cost per prescription 2008 ($)	Generic available	FDA approval date
Typical antipsychotics					
Perphenazine (Trilafon®)	0.80	0.6-1.0	12	Yes	02/57
Chlorpromazine (Thorazine®)	0.62	0.4-0.8	9	Yes	10/57
Trifluoperazine (Stelazine®)	0.26	0.2-0.4	26	Yes	04/59
Fluphenazine (Permitil®)	0.64	0.5-0.8	9	Yes	09/59
Thioridazine (Mellaril®)	0.35	0.2-0.5	11	Yes	03/62
Haloperidol (Haldol®)	2.48	2.1-2.9	13	Yes	04/67
Thiothixene (Navane®)	0.31	0.2-0.4	12	Yes	07/67
Molindone (Moban®)	-	-	-	Yes	01/74
Loxapine (Loxitane®)	-	-	-	Yes	02/75
Atypical antipsychotics					
Clozapine (Clozaril®)	1.56	1.2-1.9	85	Yes	09/89
Risperidone (Risperdal®)	12.02	10.8-13.2	200	Yes	12/93
Olanzapine (Zyprexa®)	6.15	5.4-6.9	406	No	09/96
Quetiapine (Seroquel®)	16.67	15.2-18.1	227	No	09/97
Ziprasidone (Geodon®)	2.96	2.5-3.4	308	No	02/01
Aripiprazole (Abilify®)	6.66	5.8-7.5	421	No	11/02
Paliperidone (Invega®)	0.78	0.6-1.0	345	No	12/06

*Name represents original brand name first approved by the FDA, which may differ from current most frequently reported drug name (generic or brand); missing values denote products with minimal usage in 2008; analyses excluded Symbyax; values for total prescriptions derived from the IMS Health National Disease and Therapeutic Index™, 2008; values for total prescriptions and cost per prescription derived from the IMS Health National Prescription Audit™

TABLE 2

TYPICAL AND ATYPICAL ANTIPSYCHOTIC USE STRATIFIED BY CLINICAL INDICATION.*

	1995-1996	1997-1998	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008
TYPICAL ANTIPSYCHOTICS							
Schizophrenia, %	32	36	39	45	48	50	51
Bipolar affective disorder, %	12	11	11	13	13	18	17
Depression/Reaction, %	16	14	14	14	12	7	7
Anxiety, %	4	5	3	3	4	3	3
ADHD/Conduct, %	2	2	2	2	1	1	1
Dementia, %	8	6	6	4	4	2	4
Other psychosis, %	9	11	10	8	9	9	4
All others, %	17	15	15	11	9	10	12
Total visits (thousands)	9,992	7,107	3,941	2,781	3,110	2,916	2,253
ATYPICAL							
Schizophrenia, %	51	37	32	29	24	24	24
Bipolar affective disorder, %	11	16	18	21	24	30	34
Depression/Reaction, %	15	13	18	18	17	15	14
Anxiety, %	3	4	4	5	6	5	4
ADHD/Conduct, %	2	2	3	3	5	5	5
Dementia, %	5	7	7	7	7	4	3
Other psychosis, %	8	13	11	11	10	10	9
All others, %	7	8	7	7	8	7	7
Total visits (thousands)	2,699	6,383	8,723	15,560	22,987	29,846	26,801

*Source: IMS Health National Disease and Therapeutic Index™, 1995-2008

TABLE 3

ATYPICAL ANTIPSYCHOTIC USE STRATIFIED BY AGE AND FDA LABEL STATUS.*

	1995-1996	1997-1998	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008
Younger than 18 years							
On-label, %	12	12	21	23	24	26	24
Off-label, moderate or good evidence, %	33	27	24	18	12	8	9
Off-label, uncertain evidence, %	55	61	55	58	64	66	67
Total for younger than 18, N (thousands)	120	472	977	1774	3518	4520	4216
18 to 64 years							
On-label, %	53	47	44	42	42	41	46
Off-label, moderate or good evidence, %	2	7	9	10	6	5	4
Off-label, uncertain evidence, %	44	46	47	47	52	55	50
Total for 18-64, N (thousands)	2099	4553	5787	10422	15053	20569	18634
65 years and older							
On-label, %	18	17	15	16	15	21	25
Off-label, moderate or good evidence, %	1	20	22	26	20	17	12
Off-label, uncertain evidence, %	80	63	62	57	65	63	63
Total for 65 and older, N (thousands)	358	1116	1689	2849	3517	3543	2989
All ATYPICAL visits							
On-label, %	47	39	35	35	35	36	40
Off-label, moderate or good evidence, %	4	10	13	14	9	7	6
Off-label, uncertain evidence, %	50	51	51	51	56	57	54
Total visits, N (thousands)	2577	6141	8453	15045	22088	28632	25839

*Values and column percents exclude the approximate 1%-2% of subjects whose age was not specified; Source: IMS National Disease and Therapeutic Index™, 1995-2008 and DrugDex™

TABLE 4

TYPICAL ANTIPSYCHOTIC USE STRATIFIED BY AGE AND FDA LABEL STATUS.*

	1995-1996	1997-1998	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008
Younger than 18 years							
On-label, %	14	15	16	9	44	55	45
Off-label, moderate or good evidence, %	0	0	0	0	0	0	0
Off label, uncertain evidence, %	85	85	84	91	56	45	55
Total for younger than 18, N (thousands)	608	441	232	81	77	67	31
18 to 64 years							
On-label, %	26	28	32	34	38	41	38
Off-label, moderate or good evidence, %	2	1	1	1	1	1	2
Off-label, uncertain evidence, %	73	71	67	66	61	58	61
Total for 18-64, N (thousands)	6543	4996	2601	2055	2300	2227	1675
65 years and older							
On-label, %	12	17	22	21	28	36	32
Off-label, moderate or good evidence, %	2	3	3	1	2	2	1
Off-label, uncertain evidence, %	86	80	75	79	69	62	67
Total for 65 and older, N (thousands)	2493	1472	938	565	641	495	486
All TYPICAL visits							
On-label, %	21	25	29	30	36	40	36
Off-label, moderate or good evidence, %	2	1	1	1	1	1	2
Off-label, uncertain evidence, %	77	73	70	69	63	58	62
Total visits, N (thousands)	9644	6909	3771	2701	3018	2789	2192

*Values and column percents exclude the approximate 1%-2% of subjects whose age was not specified; Source: IMS National Disease and Therapeutic Index™, 1995-2008 and DrugDex™

Pharmacotherapy for Post-traumatic Stress Disorder In Combat Veterans

Focus on Antidepressants and Atypical Antipsychotic Agents

Walter Alexander

Introduction

The U.S. Department of Veterans Affairs defines post-traumatic stress disorder (PTSD) as "the development of characteristic and persistent symptoms along with difficulty functioning after exposure to a life-threatening experience or to an event that either involves a threat to life or serious injury."[1] Patients with PTSD usually present for primary care with unexplained somatic and/or psychological symptoms, including sleep disturbances, night sweats, fatigue, and difficulty with memory or concentration (Table 1). PTSD consists of three main symptom "clusters:"[1,2]

1. *Re-experiencing.* The traumatic event is persistently re-experienced through recurrent and intrusive recollections of the trauma and through recurrent distressing dreams of the event. The patient may also act or feel as though the traumatic event were recurring and may experience intense psychological distress when exposed to reminders of the trauma.
2. *Avoidance.* The patient persistently attempts to avoid stimuli associated with the traumatic event. This can include avoiding thoughts, feelings, or conversations related to the trauma and avoiding people, activities, and places that arouse memories of the trauma.
3. *Increased arousal.* Patients may have difficulty falling or staying asleep and difficulty concentrating. They may also show irritability with outbursts of anger and may exhibit hypervigilance and an exaggerated startle response.

PTSD can be either acute or chronic. In those with acute PTSD, symptoms last for at least 1 month but less than 3 months after the traumatic event. In chronic PTSD, symptoms last for more than 3 months after exposure to trauma.[1]

The only FDA-approved drugs for the treatment of PTSD are the selective serotonin reuptake inhibitors (SSRIs) sertraline (Zoloft, Pfizer) and paroxetine HCl (Paxil, GlaxoSmithKline).[2–4] All other agents are used off-label, including paroxetine mesylate (Pexeva, Noven), which is chemically similar to paroxetine but is not FDA-approved for PTSD.[5] SSRIs affect the neurotransmitter serotonin primarily, which is important in regulating mood, anxiety, appetite, sleep, and other bodily functions.[2]

Although SSRIs are associated with an overall response rate of approximately 60% in patients with PTSD, only 20% to 30% of patients achieve complete remission.[6] In two clinical studies of PTSD, sertraline was significantly more effective than placebo, according to several efficacy measures, including the Clinician-Administered PTSD Scale, Part 2 (CAPS-2). In two additional studies, however, the difference in response to treatment between patients receiving sertraline and patients receiving placebo was not statistically significant.[3]

Table 1 Common Signs and Symptoms After Exposure to a Traumatic Event

Physical	Cognitive/Mental	Emotional	Behavioral
• Chills	• Blaming others	• Agitation	• Increased alcohol consumption
• Difficulty breathing	• Change in alertness	• Anxiety	• Antisocial acts
• Dizziness	• Confusion	• Apprehension	• Change in activity
• Elevated blood pressure	• Hypervigilance	• Denial	• Change in communication
• Fainting	• Increased or decreased awareness of surroundings	• Depression	• Change in sexual functioning
• Fatigue		• Emotional shock	• Change in speech pattern
• Grinding teeth	• Intrusive images	• Fear	• Emotional outbursts
• Headaches	• Memory problems	• Feeling overwhelmed	• Inability to rest
• Muscle tremors	• Nightmares	• Grief	• Change in appetite
• Nausea	• Poor abstract thinking	• Guilt	• Pacing
• Pain	• Poor attention	• Inappropriate emotional response	• Startle reflex intensified
• Profuse sweating	• Poor concentration		• Suspiciousness
• Rapid heart rate	• Poor decision making	• Irritability	• Social withdrawal
• Twitches	• Poor problem solving	• Loss of emotional control	
• Weakness			

Modified from the Department of Veterans Affairs and the Department of Defense.[1]

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Disclosure: The author reports no commercial or financial relationships in regard to this article.

Moreover, few published trials have demonstrated the superiority of paroxetine over placebo in managing the three symptom clusters of PTSD.[7,8] A comparison of paroxetine with placebo in patients with PTSD demonstrated that sertraline was significantly superior to placebo for the change from baseline in the CAPS-2 total score but not for the proportion of responders on the Clinical Global Impression–Improvement (CGI–I) scale.[4]

The SSRI fluoxetine (Prozac, Eli Lilly) was evaluated in a placebo-controlled study of combat veterans with severe, chronic PTSD.[9] Veterans treated with fluoxetine failed to show a greater clinical response compared with placebo-treated veterans, even though fluoxetine was effective in patients with less severe PTSD in previous studies. Fluoxetine has been on the market since 1987 and is indicated for the treatment of major depressive disorder, obsessive compulsive disorder, bulimia nervosa, and panic disorder.[10]

In a study of extended-release (ER) venlafaxine (Effexor XR, Pfizer), a serotonin–norepinephrine reuptake inhibitor (SNRI), the response rate was 78% and the remission rate was 40% (both assessed with an abbreviated version of CAPS) in patients with PTSD.[11] Hyperarousal, however, did not show significant improvement. The extended-release formulation of venlafaxine is approved for patients with major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder.[12]

The variable efficacy results reported with SSRIs and SNRIs in patients with PTSD led investigators to a search for alternative therapies. Second-generation (atypical) antipsychotic drugs have been used to treat PTSD based on limited data and theoretical mechanisms of action involving the serotonergic and dopaminergic systems, alpha-adrenergic receptors, and antihistaminic effects.[6]

This article reviews the use of SSRIs, SNRIs, and atypical antipsychotic agents in patients with combat-related PTSD.

Combat-Related Post-traumatic Stress Disorder

In a recent article, Dr. Charles W. Hoge described the conundrum of PTSD in war veterans:[13]

> The paradox of war-related PTSD is that reactions labeled 'symptoms' upon return home can be highly adaptive in combat, fostered through rigorous training and experience. For example, hyperarousal, hypervigilance, and the ability to channel anger, shut down (numb) other emotions even in the face of casualties, replay or rehearse responses to dangerous scenarios, and function on limited sleep are adaptive in war.

Among veterans with PTSD, as diagnosed by the Department of Veterans Affairs, 89% are treated with SSRIs.[14] Reductions in PTSD scores in clinical trials of SSRIs have been similar to those observed in studies of psychotherapy for PTSD.[1,15] Regardless of the treatment modality used, a high percentage of veterans who begin PTSD treatment eventually drop out. It has been estimated that no more than 20% of veterans with PTSD are effectively treated,[16] possibly because SSRIs are more effective in women than in men and because they are more effective in acute PTSD than in chronic disease.[9,17]

In an assessment of mental health problems among soldiers returning from the Iraq War, Milliken et al. screened the veterans immediately after deployment and again a few months later.[18] Upon rescreening, a large cohort of soldiers with PTSD who were missed on the initial screening were identified; it was also noted that most soldiers with significant PTSD symptoms at the initial screening subsequently improved without treatment. Of the 88,235 soldiers involved in the assessment, 14,213 (16%) were referred for mental health care. The authors noted that combat-related PTSD might represent a more refractory form of PTSD than that resulting from other types of traumatic events, perhaps because of later-emerging comorbidities.

Clinical Practice Guidelines

In 2010, the Department of Veterans Affairs and the Department of Defense (VA/DoD) updated their clinical practice guidelines for the management of post-traumatic stress.[1] These guidelines were originally issued in 2004 in an effort to bring evidence-based practice to clinicians who were treating trauma survivors and patients with stress disorders in the VA/DoD. In these guidelines, the term *post-traumatic stress* covers a spectrum of disorders, including acute stress reaction, acute stress disorder, and acute and chronic PTSD.

Although PTSD can occur alone, it usually accompanies other conditions, including persistent difficulties in interpersonal relations, mood disturbances, chronic pain, sleep disturbances, and psychiatric disorders. The guidelines' Working Group recognized the importance of comorbidities in patients with PTSD and pointed out that few clinical trials have provided guidance on how to manage PTSD accompanied by comorbid conditions, such as substance abuse.

The guidelines state that veterans who have sustained a concussion or mild traumatic brain injury in combat are at significantly greater risk for developing PTSD, which may be associated with neurocognitive impairment and other post-concussion symptoms. Not surprisingly, the frequency and intensity of combat are the strongest predictors for the development of PTSD.

The guidelines' Working Group noted that all current therapies of post-traumatic stress have limitations and urge the "creative integration of combined treatments that are driven by sound evidence-based principles." Interestingly, of the more than 100 pages that address the treatment of post-traumatic stress, fewer than 20 pages discuss pharmacotherapies.

According to the VA/DoD guidelines, there is growing evidence that PTSD is characterized by specific "psychobiologic dysfunctions," and this has contributed to an increased interest in the use of medications to treat trauma-related biologic effects. Importantly, only SSRIs and SNRIs have provided significant benefit in PTSD, according to the guidelines. The guidelines give the use of SSRIs and SNRIs in patients with PTSD an "A" recommendation, defined as follows: "A strong recommendation that clinicians provide the intervention to eligible patients. Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm."

The same level of evidence supports the guidelines' recommendation for monotherapy with the SSRIs sertraline, paroxetine, and fluoxetine, and with the SNRI venlafaxine in patients

with PTSD. As noted previously, only sertraline and paroxetine HCl have received FDA approval for the treatment of PTSD.

In 2004, the American Psychiatric Association (APA) published practice guidelines for patients with acute stress disorder and PTSD.[19] These guidelines identify SSRIs (sertraline, paroxetine, and off-label fluoxetine) as the medications of choice for patients with PTSD, for several reasons:

- They ameliorate all three PTSD symptom clusters (i.e., re-experiencing, avoidance, and hyperarousal).
- They are effective for psychiatric disorders that frequently occur with PTSD (e.g., depression, panic disorder, social phobia, and obsessive–compulsive disorder).
- They may reduce clinical symptoms (such as suicidal, impulsive, and aggressive behaviors) that often complicate the management of PTSD.
- They are associated with relatively few side effects.

The APA guidelines note that because no psychotropic medications have been developed specifically for use in PTSD, drugs have been used in doses similar to those recommended or approved for other psychiatric illnesses, both in clinical practice and in pharmacotherapy research.

Although the APA guidelines have not been formally updated, a "Guideline Watch," published in March 2009, provided additional information that became available after the guidelines were first published.[20] The authors reported that newer studies in patients with non–combat-related PTSD augment the evidence base for SSRI efficacy previously established in patients (predominantly women) with PTSD resulting from civilian trauma, including childhood and adult sexual assault, other interpersonal traumas, and motor vehicle accidents. Studies in combat veterans with PTSD, however, have reported variable responses to SSRI therapy. These findings suggest that SSRIs might not be as useful in veterans with combat-related PTSD as they are in civilian patients with PTSD.

Selective Serotonin Reuptake Inhibitors

Sertraline (Zoloft)

In early studies, sertraline demonstrated clinical efficacy in patients with PTSD and comorbid alcohol dependence,[21] in rape victims with PTSD,[22] and in patients with obsessive–compulsive disorder.[23] Based on these findings, Brady and colleagues conducted a randomized, double-blind study of sertraline in patients with chronic PTSD with a minimum duration of symptoms of 6 months.[24] A total of 187 patients were randomly assigned to receive 12 weeks of treatment with either sertraline (initiated at 25 mg/day and titrated as needed to 200 mg/day) or matched placebo.

At the end of treatment, sertraline provided significantly greater improvement in three of the four primary outcome measures (the CAPS-2 total severity score, the Clinical Global Impression–Severity [CGI–S] rating, and the CGI–I rating) compared with placebo. The reduction in the fourth primary outcome measure, the Impact of Event Scale (IES) total score, with sertraline did not reach statistical significance when compared with placebo. Similarly, sertraline significantly improved the PTSD symptom clusters of avoidance and hyperarousal, but not re-experiencing, compared with placebo. Response rates were 53% and 32% for sertraline and placebo, respectively ($P = 0.008$).

Sertraline was well tolerated; insomnia was the only adverse event reported significantly more often with sertraline than with placebo (16.0% vs. 4.3%, respectively; $P = 0.01$).

In another 12-week double-blind trial, 208 patients with moderate-to-severe PTSD were randomly assigned to receive sertraline (50 to 200 mg daily) or placebo.[25] The primary outcome measures were the CAPS-2 total severity score, the IES total score, the CGI–S rating, and the CGI–I rating. After 12 weeks of treatment, sertraline provided significantly greater improvement on all four primary outcome measures compared with placebo. Sertraline also improved all three PTSD symptom clusters versus placebo. The response rates were 60% in the sertraline group and 38% in the placebo group ($P = 0.004$).

Sertraline was associated with significantly higher rates of insomnia, diarrhea, nausea, and decreased appetite compared with placebo. Discontinuation rates were 39% for sertraline and 27% for placebo. Withdrawals attributed to adverse events occurred in 9.1% of sertraline-treated patients and in 4.7% of placebo-treated patients. The corresponding rates of withdrawal resulting from an insufficient therapeutic response were 0% and 4.7%, respectively.

A double-blind placebo-controlled study evaluated sertraline in 42 Israeli military veterans with combat-induced PTSD.[26] The subjects received either sertraline (50 to 200 mg/day) or placebo for 10 weeks. Treatment efficacy was determined by CAPS-2 and by CGI–S and CGI–I ratings. Therapy with sertraline resulted in numeric, but not statistically significant, improvements in CAPS-2 total severity and symptom-cluster scores versus placebo. CGI–I responder rates were 53% for sertraline and 20% for placebo ($P = 0.057$). Thirteen percent of the sertraline group discontinued treatment because of adverse events.

Paroxetine (Paxil)

Paroxetine, the other SSRI approved for the treatment of PTSD, was evaluated in 551 patients with chronic PTSD.[27] The patients were randomly assigned to receive 12 weeks of treatment with paroxetine (20 mg/day), paroxetine (40 mg/day), or placebo. CAPS-2 and CGI–I scores were used to assess efficacy. Both dosages of paroxetine achieved significant improvements in the primary outcome measures compared with placebo. The mean changes from baseline in CAPS-2 were –39.6 and –37.9 for paroxetine (20 mg/day and 40 mg/day, respectively), compared with a mean change of –25.3 for placebo ($P = 0.001$). In addition, all three symptom clusters of PTSD were significantly improved with paroxetine compared with placebo ($P = 0.0001$). Significantly more paroxetine-treated patients at both doses were rated as responders compared with the placebo-treated group (65% and 55% vs. 35%, respectively; $P < 0.001$).

Paroxetine was well tolerated. The most commonly reported adverse events associated with paroxetine use (with an incidence of at least 10% and twice that of placebo) were asthenia, diarrhea, abnormal ejaculation, impotence, nausea, and somnolence.

Tucker et al. compared flexible dosages of paroxetine (20 to 50 mg/day) with placebo in 307 outpatients with PTSD.[28]

After 12 weeks of treatment, the paroxetine group showed significantly greater improvements in PTSD symptoms, compared with the placebo group, on all primary and secondary outcome measures. In addition, more patients who were treated with paroxetine achieved a response (60% vs. 40%, respectively; $P < 0.05$) and remission (30% vs. 20%, respectively; $P = 0.008$).

Fluoxetine (Prozac)

Although fluoxetine is recommended as a first-line (off-label) therapy in PTSD,[1,19] efficacy results from clinical trials have been variable. For example, Connor et al. reported a superior response with fluoxetine in civilian patients with PTSD,[29] and Meltzer-Brody et al. observed that fluoxetine reduced all symptom clusters of the disorder in civilians.[30] Martenyi et al., however, found that fluoxetine did not differ significantly from placebo in civilian patients with PTSD.[31]

Similarly, Hertzberg et al. reported that fluoxetine lacked efficacy, compared with placebo, in combat veterans with PTSD,[9] whereas Martenyi et al. noted that fluoxetine was significantly superior to placebo in veterans.[32,33]

Serotonin–Norepinephrine Reuptake Inhibitors

Venlafaxine

Like fluoxetine, the SNRI venlafaxine is not approved for the treatment of PTSD, but it is often used off label as first-line monotherapy in these patients.[1,2] Venlafaxine acts primarily as a serotonin reuptake inhibitor (SRI) at lower dosages and as a combined serotonin–norepinephrine reuptake inhibitor (SNRI) at higher dosages.[2]

Extended-release (ER) venlafaxine was shown to be effective in two trials involving more than 800 patients with non–combat-related PTSD.[11,34] In a long-term double-blind study, 329 adult outpatients with PTSD were randomly assigned to receive venlafaxine ER (37.5–100 mg/day) or placebo for 6 months.[11] Venlafaxine ER provided a significant change in CAPS total scores when compared with placebo (–51.7 vs. –43.9, respectively; $P = 0.006$). Remission rates were 50.9% for venlafaxine ER and 37.5% for placebo ($P = 0.01$). Venlafaxine ER also significantly improved cluster scores for re-experiencing ($P = 0.008$) and for avoidance ($P = 0.006$) but not for hyperarousal. The authors theorized that drugs with noradrenergic-enhancing effects might promote arousal.

In another double-blind study, venlafaxine ER performed as well as sertraline in adult outpatients with PTSD.[34] A total of 538 patients were randomly assigned to receive venlafaxine ER (37.5–100 mg/day), sertraline (25–200 mg/day), or placebo for 12 weeks. Mean changes in CAPS symptom-cluster scores were –41.8, –39.4, and –33.9 for venlafaxine ER, sertraline, and placebo, respectively.

The difference between venlafaxine ER and placebo was statistically significant ($P < 0.05$). Both active treatments provided significant improvements in avoidance compared with placebo, but only venlafaxine ER differed significantly from placebo in improving hyperarousal. The two active treatments were no better than placebo in improving re-experiencing. Remission rates were 30.2% for venlafaxine ER ($P < 0.05$ vs. placebo), 24.3% for sertraline, and 19.6% for placebo.

Atypical Antipsychotic Agents

Although second-generation (atypical) antipsychotic agents were originally developed to treat psychotic disorders, they are also used in patients with other psychiatric disorders, including PTSD. These drugs act primarily on the dopaminergic and serotonergic systems. Clinical studies have indicated that they are useful in ameliorating psychotic symptoms in patients with PTSD.[2]

A review of the use of off-label antipsychotic medications in the VA health care system found that 60.2% of patients who received an antipsychotic drug had no record of a diagnosis for which these drugs are approved.[35] Prescriptions for off-label antipsychotic agents were most often written for PTSD (41.8% of patients). Quetiapine (Seroquel, AstraZeneca) had the greatest off-label use (42.9%), followed by risperidone (Risperdal, Janssen) (21.2%). Relatively few patients received off-label olanzapine (Zyprexa, Eli Lilly) (7.5%).

Quetiapine (Seroquel)

Quetiapine, a dibenzothiazepine derivative, is indicated for the treatment of schizophrenia and bipolar disorder. Its precise mechanism of action is unknown. However, the drug's clinical activity is believed to be mediated through a combination of dopamine type-2 (D_2) and serotonin type-2 ($5\text{-}HT_2$) antagonism.[36]

Quetiapine monotherapy was evaluated in an open-label study of veterans with combat-related PTSD with psychotic features.[37] A total of 53 veterans were treated with quetiapine (25–400 mg/day) for 8 weeks. A reduction in total and subscale scores on CAPS was a primary outcome measure, and CGI–S scores were used to assess global clinical improvement. Quetiapine reduced the majority of the psychotic and PTSD symptoms in these patients, as indicated by significant reductions in CAPS scores and CGI–S ratings.

In another open-label study, Ahearn et al. added quetiapine to sertraline in 15 patients with severe PTSD; 10 patients had combat-related PTSD, and the remaining five patients had non–combat-related PTSD.[38] The patients received quetiapine (mean dosage, 216 mg/day) for 8 weeks. The addition of quetiapine to SSRI therapy resulted in a 42% overall improvement in PTSD symptoms, based on CAPS scores, and significant improvements in re-experiencing ($P = 0.0012$), avoidance ($P = 0.03$), and hyperarousal ($P = 0.001$).

In a prospective study, Sokolski et al. reviewed medical charts to evaluate the effects of adjunctive quetiapine therapy in 68 Vietnam War veterans with treatment-resistant, combat-induced PTSD.[39] The investigators found that the addition of quetiapine to ongoing therapy had resulted in further symptomatic improvements in re-experiencing, avoidance, and hyperarousal in 35%, 28%, and 65% of the veterans, respectively. Low doses of quetiapine (mean dose, 155 mg) were associated with minimal adverse effects.

Hamner et al. enrolled 18 veterans with combat-related PTSD who had shown an inadequate response to other medications into an open-label study of adjunctive quetiapine.[40] Treatment at 25 to 300 mg/day for 6 weeks resulted in a significant improvement in CAPS scores, from 89.8 to 67.5 ($P < 0.005$). General psychopathology and depressive symptoms were also reduced.

Risperidone (Risperdal)

Risperidone, a benzisoxazole derivative, is used primarily to treat schizophrenia. Its precise mechanism of action is unknown. However, its therapeutic activity in schizophrenia is believed to be mediated through a combination of D_2 and 5-HT_2 antagonism.[41,42]

A prospective, randomized, double-blind, placebo-controlled study was conducted to investigate the potential efficacy of risperidone in treating the psychotic symptoms of chronic PTSD in 40 combat veterans.[43] Thirty-seven veterans completed at least 1 week of treatment with risperidone or placebo during the 5-week follow-up period. The investigators assessed symptoms according to CAPS and the Positive and Negative Syndrome Scale (PANSS) scores.

Veterans receiving risperidone showed a significantly greater decrease in psychotic symptoms, as indicated by PANSS scores, compared with placebo-treated veterans ($P < 0.05$). Both groups experienced declines in CAPS scores, but these differences were not statistically significant. The risperidone-treated veterans, however, had significantly greater improvements in re-experiencing at week 5 compared with the placebo-treated group ($P < 0.05$).

In a recent VA study, risperidone was no more effective than placebo in 296 veterans with treatment-resistant, combat-related PTSD.[44] The CAPS score was the primary outcome measure. Changes in CAPS score from baseline to 6 months were –16.3 in the risperidone group compared with –12.5 in the placebo group ($P = 0.11$). Moreover, risperidone did not reduce symptoms of depression or anxiety compared with placebo.

Adverse events were more common with risperidone, including weight gain, fatigue, somnolence, and hypersalivation.

Olanzapine (Zyprexa)

Olanzapine, a member of the thienobenzodiazepine class, is approved for the treatment of schizophrenia and bipolar I disorder. As with other drugs used to treat schizophrenia, its precise mechanism of action is unknown. However, as with risperidone, its efficacy in schizophrenia is believed to be mediated through a combination of dopamine and serotonin antagonism.[45]

In a double-blind, placebo-controlled pilot study, olanzapine was no more effective than placebo in patients with PTSD.[46] Fifteen patients received olanzapine (5–20 mg/day) or placebo for 10 weeks. Both treatment groups showed improvement in PTSD symptoms, but there were no between-group differences in treatment response.

In an open-label study, Petty et al. administered olanzapine for 8 weeks to 48 veterans with combat-induced PTSD;[47] 30 veterans completed the study. All primary and secondary outcomes measures, including CAPS and CGI–I scores, improved significantly during treatment, indicating that olanzapine was useful for treating the symptoms of combat-related PTSD.

In another open-label trial, olanzapine was compared with fluphenazine (Prolixin, Apothecon), a first-generation antipsychotic drug, in combat veterans with PTSD.[48] Pivac et al. gave 55 veterans olanzapine or fluphenazine in a range of 5 to 10 mg/day, once or twice daily, for 6 weeks. Olanzapine was more effective than fluphenazine in reducing most psychotic and PTSD symptoms and was better tolerated. Prolonging treatment for an additional 3 weeks did not affect the efficacy of either drug.

Other studies have looked at olanzapine as adjunctive therapy for combat veterans with PTSD. In one report, olanzapine alleviated nightmares and insomnia when it was added to current therapies in veterans with treatment-resistant, combat-induced PTSD.[49] In another study, olanzapine provided significant reductions in measures of post-traumatic stress, depression, and sleep disorder versus placebo in patients with SSRI-resistant, combat-related PTSD.[50]

Adjunctive olanzapine has also improved chronic sleep disruption and the re-experiencing cluster of symptoms in civilian patients with PTSD presenting for primary care.[51]

Veterans Affairs and Defense Department Guidelines Updated

The VA/DoD clinical practice guidelines originally recommended off-label risperidone, olanzapine, or quetiapine for the adjunctive treatment of patients with PTSD.[1] However, in view of the disappointing results from the recent VA-sanctioned study of risperidone in PTSD,[44] the guidelines have been revised to recommend against the use of risperidone as adjunctive therapy.[52] The revised guidelines further state that "there is insufficient evidence to recommend for or against the use of any other atypical antipsychotic as an adjunctive therapy for the treatment of PTSD."

Table 2 depicts the VA/DoD's current assessment of the drugs used to treat PTSD (see page 37).[52]

Despite the lack of a clear benefit with risperidone in the VA-supported study and the lack of sufficient evidence supporting the use of any other atypical antipsychotic drug in PTSD, it is too soon to close the door on these agents in patients with PTSD. Some studies have suggested differential effects between atypical antipsychotic medications, and head-to-head comparative trials have not been conducted. Further, the unmet clinical need in PTSD, based on the partial remission rates with other classes of agents, remains substantial.

Ongoing Studies of Atypical Antipsychotic Agents

Additional information on the use of atypical antipsychotic drugs in patients with PTSD is forthcoming. Two studies with quetiapine have been completed, and manuscripts are in preparation.

The first investigation evaluated adjunctive treatment with quetiapine in 80 patients (mostly combat veterans) with treatment-resistant, chronic PTSD.[53] The patients received 12 weeks of therapy with quetiapine or placebo, and the CAPS score served as the primary efficacy measure. Mark Hamner, MD, Professor of Psychiatry at the Medical University of South Carolina, Charleston, was the principal investigator.

The second study, in which Dr. Hamner also participated, initially assessed the results of 8 weeks of treatment with paroxetine in combat veterans with PTSD.[53] A total of 102 nonresponders were then assigned to receive 8 weeks of additional therapy with quetiapine. The CAPS score again served as the primary endpoint.

Table 2 Assessment of Pharmacotherapeutic Interventions for Post-traumatic Stress Disorder in War Veterans

Significant Benefit	Some Benefit	Unknown Benefit	No Benefit
• SSRIs • SNRIs	• MAO inhibitors (phenelzine) [caution*] • Mirtazapine • Nefazodone [caution*] • Prazosin (for sleep/nightmares) • TCAs	• Atypical antipsychotics (monotherapy) • Atypical antipsychotics (adjunctive) • Bupropion • Buspirone • Clonidine • Conventional antipsychotics • Gabapentin • Lamotrigine • Non-benzodiazepine hypnotics • Prazosin (for global PTSD) • Propranolol • Trazodone (adjunctive)	• Benzodiazepines [harmful] • Guanfacine • Risperidone • Tiagabine • Topiramate • Valproate

* Attention to drug-drug and dietary interactions.

MAO = monoamine oxidase; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin–norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

Adapted from the Department of Veterans Affairs and the Department of Defense.[52]

Conclusion

PTSD is a severe and chronic anxiety disorder, with impairment in daily functioning, frequent suicidal behavior, and high rates of comorbidity. SSRIs are considered first-line therapy for PTSD, in view of treatment guideline recommendations and the results of numerous clinical trials. Sertraline and paroxetine are the only antidepressants approved by the FDA for the treatment of PTSD and are the most extensively studied SSRIs for this indication. All other agents are used in an off-label fashion. In addition to sertraline and paroxetine, the SSRI fluoxetine has been recommended as first-line treatment (off label) for patients with PTSD.

If SSRIs are not tolerated or are ineffective, SNRIs should be considered as a second-line treatment. The SNRI venlafaxine has been shown to be beneficial in the treatment of PTSD.

Although atypical antipsychotics are not FDA-approved for the treatment of PTSD, they may have a role in severe cases of the disorder or when psychotic symptoms are prominent.

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Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2009 March 17; 33(2): 169–180. doi:10.1016/j.pnpbp.2008.12.004.

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CONFLICT OF INTEREST

Drs Berger, Mendlowicz, Marques-Portella, Figueira, Fontenelle and Marmar have no conflicts of interest. Dr. Kinrys has received research grants and support from AstraZeneca, Bristol-Myers Squibb, CNS Response, Cephalon, Elan, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Pfizer, Sanofi-Aventis, Sepracor, Takeda, and UCB Pharma.

Pharmacologic Alternatives to Antidepressants in Posttraumatic Stress Disorder: A Systematic Review

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Abstract

The selective serotonin reuptake inhibitors (SSRIs) are considered the first-line pharmacological treatment for PTSD. However, even when treated with this class of drugs, response rates rarely exceed 60% and less than 20–30% of the patients achieve full remission. The aim of this study was to address this limitation by systematically reviewing the options left for the treatment of PTSD when patients do not respond satisfactorily to or tolerate SSRIs. A systematic review covering all original articles, letters and brief reports published in any language until October 2008 was conducted through searches in the ISI/Web of Science, PubMed and PILOTS databases. The search terms included the pharmacological class of each agent or its generic name plus “PTSD” or “stress disorder” in the title, in the abstract or as a keyword. Sixty-three articles were selected, covering the following categories: antipsychotics, anticonvulsants, adrenergic-inhibiting agents, opioid antagonists, benzodiazepines and other agents. None of the identified agents reached the level A of scientific evidence, 5 reached level B, 7 level C and 13 level D. The non-antidepressant agent with the strongest scientific evidence supporting its use in PTSD is risperidone, which can be envisaged as an effective add-on therapy when patients did not fully benefit from previous treatment with SSRIs. Prazosin, an adrenergic-inhibiting agent, is a promising alternative for cases of PTSD where nightmares and insomnia are prominent symptoms. So far, there is no consistent empirical support for using benzodiazepines in the prevention or in the treatment of PTSD, although these drugs could alleviate some associated non-specific symptoms, such as insomnia or anxiety. Further controlled clinical trials and meta-analysis are needed to guide clinicians in their search of effective pharmacological alternatives to antidepressants in PTSD.

Keywords

Pharmacologic treatment; posttraumatic stress disorder; PTSD; refractory; systematic review

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a pathological response to a traumatic event that is characterized by the presence of three clusters of symptoms: reexperiencing (cluster B), avoidance/numbing (cluster C), and hyperarousal (cluster D). The symptoms must last for a minimum of one month and disrupt functioning. If the symptoms persist for more than three months, then PTSD is considered to be chronic (American Psychiatric Association 1994).

The treatment of PTSD has several specific goals: to reduce the severity of symptoms, to prevent and/or treat comorbid disorders, to decrease functional impairment, to modify pathogenic fear schemas, to prevent relapse, to build resilience and to improve quality of life (Ursano *et al.* 2004). The most common definitions of treatment response in PTSD patients are a decrease of 30% or more (Hamner *et al.* 2004) in the *Clinician Administered PTSD Scale* (CAPS) score (Blake *et al.* 1990) or a score of 1 ("very much") or 2 ("much improved") (Stein *et al.* 2006) in the Clinical Global Impressions scale - Improvement item (CGI-I) (Guy 1976).

The selective serotonin reuptake inhibitors (SSRIs), especialy paroxetine and sertraline, are considered the first-line pharmacotherapeutic treatment for PTSD (Schoenfeld *et al.* 2004; Ursano *et al.* 2004; Asnis *et al.* 2004). However, even when treated with this class of drugs, response rates rarely exceed 60% and less than 20–30% of the patients achieve full remission (Stein *et al.* 2002; Zohar *et al.* 2002). A 6-month long double-blind, placebo-controlled study conducted by Davidson et al. (2006) found that 78% of PTSD patients treated with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine ER presented a positive clinical response (a decrease of ≥ 30% in the CAPS scores) but, nevertheless, only 40.4% of the completers achieved remission (CAPS score ≤ 20). Furthermore, treatment with venlafaxine ER failed to significantly ameliorate hyperarousal symptoms. Even considering the SSRIs, the most studied class of drugs, only two studies were able to demonstrate the superiority of paroxetine over placebo on all the three clusters of PTSD (Ballenger 2004; Tucker *et al.* 2001). These findings may reflect an intrinsic limitation of SSRIs or SNRIs in ameliorating the heterogeneous symptoms of PTSD (Davidson *et al.* 2006). In spite of that, there are relatively few studies concerned with orienting clinicians about the benefits of combining or switching medications to manage patients with PTSD who did not respond adequately to first-line treatments (Kinrys *et al.* 2006).

The aim of this study was to address this limitation by systematically reviewing the therapeutic options left for the treatment of PTSD when patients do not respond satisfactorily to or tolerate SSRIs and SNRIs. This review will focus on the following categories of pharmacological agents: antipsychotics, anticonvulsants, adrenergic-inhibiting agents, opioid antagonists, benzodiazepines and other medications.

METHODS

A systematic review covering all original articles, letters and brief reports published in any language until October 2008 was conducted through searches in the ISI/Web of Science, PubMed and PILOTS databases. The search terms included the pharmacological class of each agent (e.g. anticonvulsant*, or alpha-antagonist*) or its generic name (e.g. topiramate) plus “PTSD” or “stress disorder” in the title, in the abstract or as a keyword. The reference lists of retrieved articles were further scanned for additional relevant papers. Duplicate articles, reports on the efficacy of antidepressants in PTSD or case reports with less than five patients were preliminarily excluded. Whenever the authors of the present review had doubts about the methods or the results described in an article (i.e.if the drug was used as monotherapy), an e-mail was sent to the investigators requesting a clarification on the issue.

RESULTS

One thousand, five hundred and eighty-three articles, letters and notes were identified: 404 on antipsychotics, 285 on anticonvulsants, 390 on adrenergic-inhibiting agents, 69 on opioid antagonists, 234 on benzodiazepines, and on 201 other agents. After applying the exclusion criteria, sixty-three articles were selected and categorized according to the methodology,

design, level of scientific evidence and clinical relevance (US Department of Health an Human Services 1993), as follows:

- **A.** Multiple double-blind placebo-controlled trials with *positive* results and a confirmatory metanalysis (in addition to level B of evidence).
- **B.** At least one double-blind placebo-controlled trial with *positive* results (in addition to level C of evidence).
- **C.** Anecdotal reports, case series and open trials with *positive* results, in addition to expert endorsement or consensus.
- **D.** Few case reports with *positive* results, however without any expert panel endorsement.

The fully worked out results of our search are depicted in Table 1. Considering the critical relevance of the randomized clinical trials (RCTs) for the advancement of scientific knowledge in clinical psychopharmacology, the main characteristics (type of drugs, sample size, duration of the study, instruments employed, etc) of each of the available RCTs are featured in Table 2. Studies using less accurate methods, such as case reports and open trials were briefly summarized in the text below.

1. Antipsychotics

Although antipsychotics were not originally developed for the treatment of anxiety disorders, they are supposed to ameliorate PTSD symptoms through several mechanisms. Atypical antipsychotics (APs) act on serotonergic and dopaminergic systems, both of which have been implicated in the pathogenesis of PTSD (Eidelman *et al.* 2000; Hamner *et al.* 2003a). Some APs also show affinity for alpha-adrenergic receptors (Richelson 1996), which have been demonstrated to be dysregulated in PTSD (Nutt 2000; Raskind *et al.* 2000). In addition, due to antihistaminic effects, APs may alleviate insomnia and other sleep-related PTSD symptoms. Finally, some authors suggest that APs can reduce the cognitive and perceptual distortions in cases of PTSD with psychotic features (Butler *et al.* 1996).

LEVEL OF EVIDENCE B

1.1 Risperidone: ***Randomized Clinical Trials:*** Out of the six RCTs that have investigated the efficacy of risperidone in PTSD, only Padala and colleagues' study (2006) has demonstrated its superiority over placebo as a monotherapy. Three RCTs also showed that risperidone as an adjunctive treatment was superior to placebo in decreasing the severity of PTSD symptoms (Bartzokis *et al.* 2005; Monnelly *et al.* 2003; Reich *et al.* 2004). None of these studies, however, found risperidone to be efficacious in alleviating avoidant behavior or emotional numbness. Hamner and colleagues failed to demonstrate any advantage of risperidone over placebo as an adjunctive therapy. It must be noted, nonetheless, that their findings were based on a short trial (5 weeks) conducted in a relatively small sample of war veterans (N=37) suffering from PTSD with psychotic symptoms (Hamner *et al.* 2003b). Similarly, Rothbaum *et al.* (2008) did not find any substantial diferences among 20 civilian patients with refractory PTSD who received placebo or risperidone for 8 weeks as an adjunctive therapy after a 8-week open trial with sertraline, with only the insomnia being significantly alleviated in the risperidone-treated group.

Open Label Studies: Kozaric-Kovacic *et al.* (2005) treated 26 war veterans with refractory chronic PTSD and psychotic symptoms with risperidone (1–4 mg/day) as a monotherapy for 6 weeks. The *Positive and Negative Symptoms Scale* (PANSS) (Kay *et al.* 1987), the *PTSD Interview* (PTSD-I) (Watson *et al.* 1991), and the *Clinical Global Impressions – Severity of Illness Scale* (CGI-S) (Guy 1976) were administered at baseline, third week and endpoint. All outcome measures and respective subscales showed significant decrease ($p<0.05$) from

baseline to the third week of treatment; however, no further improvement was observed thereafter.

A 12-week open label study carried out by David *et al.* (2004) investigated the efficacy of risperidone (mean: 2.3 mg/day) as adjunctive therapy in 17 war veterans with refractory PTSD. The primary outcome measures were the CAPS (Blake *et al.* 1990) and the PANSS scores. Following treatment initiation, a significant decrease in PANSS total scores ($p=0.002$) and in each of its subscales was observed. CAPS total scores were also reduced ($p=0.03$) as were all CAPS subscales, except for the avoidant behavior/emotional numbness one. A secondary analysis conducted by the same group (David *et al.* 2006) demonstrated that risperidone was also efficacious as a adjunctive therapy for the treatment of the awakenings caused by trauma-related nightmares.

1.2 Olanzapine: ***Randomized Clinical Trials:*** We identified two RCTs with conflicting results (table 2). Butterfield *et al.* (2001) employed the *Treatment Outcomes PTSD Scale* (TOP-8) (Connor and Davidson 1999) and the *Short PTSD Rating Interview* (SPRINT) (Connor and Davidson 2001) as outcome measures to assess the efficacy of olanzapine monotherapy in non-combat-related PTSD, but did not find it to be superior to placebo. Stein *et al.* (2002) compared the efficacy of adjunctive olanzapine and placebo in an 8-week trial with traumatized war veterans and found a significant decrease in the CAPS mean total scores with active medication. Patients who received olanzapine also showed significant improvement in sleep patterns. There were, however, no differences between the two groups in the *Clinical Global Impression* (CGI) final scores.

Open Label Studies: In a 6-week open label trial, Pivac *et al.* (2004) compared the efficacy of olanzapine monotherapy (5–10 mg/day, n=28) with that of fluphenazine (n=27) in patients suffering from chronic, refractory combat-related PTSD. Treatment with either drug was associated with significant reductions on weeks 3 and 6 in the scores of the PTSD-I subscales of reexperiencing, avoidant behavior, and autonomic arousal ($p<0.001$), in the scores of all subscales of the PANSS, and in CGI-S scores ($p<0.05$). The authors pointed out, however, that after 3 and 6 weeks of treatment the effects of olanzapine were superior to those of fluphenazine ($p<0.05$) in the avoidant and autonomic arousal subscales of the PTSD-I, in some specific PANSS subscales (negative symptoms, general psychopathology, and supplemental items), and in the CGI-S scores.

Petty *et al.* (2001) treated 48 PTSD combat veterans with olanzapine for 8 weeks and found a significant reduction in total scores of the CAPS and in the CGI.

Anecdotal Reports and Case Series: Two case series (Jakovljevic *et al.* 2003; States and St.Dennis 2003) reported a quick improvement of insomnia and nightmares in patients with civilian and combat-related refractory PTSD after the adding of olanzapine (2.5–20 mg/day) to their therapeutic schemes.

LEVEL OF EVIDENCE C

1.3 Quetiapine: ***Open Label Studies:*** In a 6-week open label study, Hamner and colleagues (Hamner et al. 2003a) evaluated the efficacy of quetiapine (25–300 mg/day) as an adjunctive therapy on 18 patients suffering from refractory combat-related PTSD. As early as the second week of treatment, a statistically significant reduction on the mean total scores of the CAPS-2 (Blake *et al.* 1990) ($p<0.002$) was observed which became more pronounced by the end of the study ($p<0.0005$). All PTSD symptom clusters improved, especially the B one. In a secondary analysis carried out by the same group (Robert *et al.* 2005), quetiapine was found to increase sleep quality and duration, while reducing vivid dreams and nightmares.

Ahearn and colleagues (Ahearn *et al.* 2006) investigated the efficacy of quetiapine (mean: 216 mg/day) as an adjunctive treatment in 15 civilian and veteran patients with refractory PTSD. After eight weeks of treatment, significant decreases were seen in the CAPS global (42%) and symptoms clusters scores. Significant reductions were also noted in the scores of the *Davidson Trauma Scale* (DTS) (Davidson *et al.* 1997) (45%) and of the *Sheehan Disability Scale* (Leon *et al.* 1992) (44%), a scale that assesses functional impairment.

Stathis and colleagues (Stathis *et al.* 2005) treated with quetiapine monotherapy (50–200 mg/day) six juveniles suffering from PTSD and living in a youth detention center. After six weeks, a significant reduction in the scores of the *Traumatic Symptom Checklist in Children* (TSCC) (Briere 1996) was observed ($p<0.01$). Quetiapine was found to be particularly effective in the treatment of sleep problems, dissociative symptoms, anxiety, depression, and anger.

Anecdotal Reports and Case Series: Filteau *et al.* (2003) reported that the use of quetiapine (150–200 mg/day) as an adjunctive treatment in 5 patients with refractory PTSD (3 due to combat situations and 2 resulting from rape) led to a marked reduction in the flashbacks. All patients had been treated previously with venlafaxine or with an SSRI in association with either gabapentin or lamotrigine but with unsatisfactory results.

EVIDENCE LEVEL D

1.4 Clozapine: ***Open Label Studies:*** Wheatley *et al.* (2004) used clozapine (600–800 mg/day) as a monotherapy to treat 6 teenagers involuntarily committed to a forensic hospital. All patients suffered from chronic PTSD with psychotic features resulting from sexual abuse. Three patients had comorbid schizoaffective disorder and two major depression. Although no specific instruments were employed to assess PTSD, a marked improvement was found when the *Brief Psychiatric Rating Scale* (BPRS) (Overall and Gorham 1988) scores obtained during the six-month period following the treatment with clozapine were compared to those of the six-month period preceding it; aggressiveness and self-mutilatory behavior also decreased significantly.

1.5 Aripiprazole: ***Anecdotal Reports and Case Series:*** Lambert (2006) treated five war veterans with PTSD with aripiprazole (15–30 mg/day) as an augmentation strategy. Four of them reported improved sleep patterns and reduced frequency of nightmares, while the last one experienced worsening of these symptoms.

2. Anticonvulsants

The phenomenon of kindling (repeated subthreshold stimulation of regions of the central nervous system making the neurons more reactive to low-intensity stimuli) has been demonstrated in limbic regions, including the amygdala (Cullen and Goddard 1975), a structure that is linked to emotions like fear and to reactions to stress (Albucher and Liberzon 2002). Given the well-known anti-kindling properties of the anticonvulsants (Iancu *et al.* 2002), it would be reasonable to presume that they might turn out to be useful in the treatment of PTSD.

Some anticonvulsants, like valproate, enhance GABAergic and serotonergic neurotransmission, and could be expected to be effective in the treatment of anxiety, depression, hyperarousal, and intrusive thoughts (Otte *et al.* 2004). Others, like lamotrigine, which inhibits glutamatergic neurotransmission, have been shown to have antidepressant properties in bipolar depression (Jefferson 2005; Schaffer *et al.* 2006). Finally, valproate and carbamazepine have been demonstrated to be useful in the treatment of some of the most disturbing symptoms associated with PTSD, like increased irritability and aggressiveness.

EVIDENCE LEVEL B

2.1 Valproic acid: ***Randomized Clinical Trials:*** In the only RCT found comparing the efficacy of divalproex as a monotherapy (mean: 2,309 mg/day) with placebo, Davis *et al.* (2008) treated 82 veterans suffering from PTSD for 8 weeks, but did not find any significant difference between the groups, as assessed by four differents outcome measures.

In a study by Steiner and colleagues (Steiner *et al.* 2007), 12 male youth with PTSD and conduct disorder involuntarily committed to the California Youth Authority were blindly randomized to receive, after a one-week washout period, either a high (between 500–1500 mg/day) or a low dose (up to 250 mg/day) of divalproex sodium monotherapy for seven weeks. At the end of the study, 88% of the subjects medicated with high doses were rated (using the CGI) as markedly improved as against none of those on the low-dose scheme ($p<0.016$). Given that this study did not include a control group treated with placebo it was not included in Table 2.

Open Label Studies: Fesler (1991) medicated 16 war veterans with PTSD with adjunctive valproate for 2 to 17 months (average: 13.6 months). Ten patients (62.5%) reported marked improvement, particularly in symptoms of hyperarousal and, to a lesser degree, of avoidance.

Clark and colleagues (Clark *et al.* 1999b) administered divalproex, either as monotherapy (5 patients) or as an adjunctive treatment (11 patients) (1,000–2,500 mg/day; mean: 1,365 mg/day), to combat veterans with PTSD. After 8 weeks, eleven (84.6%) patients had CGI scores of 1 (markedly improved) or 2 (much improved). The CAPS sub-scores revealed a more substantial improvement in the reexperiencing and in the hyperarousal domains.

Petty *et al.* (2002) treated 14 war veterans with PTSD with valproate as a monotherapy (1,000–2,500 mg/day; mean: 1,850 mg/day) for 8 weeks. At the end of the trial, 43% of participants showed a reduction of at least 30% in the global score of CAPS, with comparable improvements observed in each of the three symptom clusters.

Divalproex (mean: 1,500 mg/day) was also employed in an eight-week trial (Goldberg *et al.* 2003) with civilian patients as a monotherapy (1 patient) and as an adjunctive treatment (6 patients) leading to a significant reduction in the symptoms of PTSD ($p<0.02$), particularly those of the avoidance and hyperarousal clusters, as measured by the *Posttraumatic Stress Disorder Symptoms Scale–Self Report* (PSS-SR) (Foa *et al.* 1993).

In a retrospective study, Davis *et al.* (2005) found that half of their fifty war veterans with PTSD treated with divalproate (three of them as monotherapy) achieved a final CGI score of ≤ 2 at the end of the therapeutic trial.

2.2 Lamotrigine: ***Randomized Clinical Trials:*** Hertzberg *et al.* (1999) administered lamotrigine as a monotherapy (mean: 380 mg/day) or placebo to 14 combat veterans and civilian patients for 12 weeks. Out of the 10 patients who were treated with lamotrigine, 5 (50%) were considered much or very much improved according to the *Physician Administered Duke Global Rating for PTSD Scale* (DGRP) (Davidson *et al.* 1998), as compared to 1 out of 4 (25%) who received placebo. Symptoms from the clusters B and C, in particular, showed marked reduction after treatment with lamotrigine. Given the small number of patients studied, however, these results must be taken with caution.

EVIDENCE LEVEL C

2.3 Carbamazepine: ***Open Label Studies:*** Looff and colleagues (Looff *et al.* 1995) treated 28 children and teenagers victims of sexual abuse with carbamazepine (300–1,200 mg/day). After 18 months, 22 patients (78.5%) were in full remission and the rest showed marked improvements, according to the subjective assessment of the research team,

Ten patients with PTSD were treated by Lipper *et al.* (1986) with carbamazepine for 5 weeks. At the end of the trial, 7 patients had CGI scores of 1 (markedly improved) or 2 (much improved). The symptoms of the reexperiencing cluster were the most improved.

Wolf *et al.* (1988) treated 10 combat veterans with carbamazepine and reported, based on the researchers' clinical judgement and the patients' self-report, a considerable improvement in impulsivity and in aggressiveness.

2.4 Topiramate: ***Randomized Clinical Trials:*** In a recent 12-week RCT, Tucker *et al.* (2007) assessed the efficacy of topiramate monotherapy (25–400 mg/day, mean: 150 mg/day) in 19 civilian patients with chronic PTSD who were compared to an equal number of patients receiving placebo. There were no significant differences between the groups in terms of the total scores of the CAPS, DTS and CGI. Topiramate-treated patients exhibited a significant decrease in reexperiencing symptoms (CAPS cluster B) and in TOP-8 scores at endpoint. Remission (defined here as CAPS total score <20) was achieved in twice as many patients in the topiramate-treated group (n=8, 42%) as compared to the placebo group (n=4, 21%).

In a 7-week, double-blind, randomized comparison of the efficacy of adjunctive topiramate and placebo for the treatment of chronic PTSD in veterans (Lindley *et al.* 2007), no differences were found between the groups. Besides, the topiramate-treated patients had a high drop-out rate (55%), mainly due adverse effects.

Open Label Studies: Berlant and van Kammen (2002) described a naturalistic data review of medical records of 35 civilian patients with chronic PTSD who were treated with topiramate (12.5–500 mg/day), either as a monotherapy (7 patients) or as an adjunctive treatment (28 patients). After four weeks, not only a significant reduction in the scores of the *Posttraumatic Checklist - Civilian Version* (PCL-C) (Weathers *et al.* 1993) ($p<0.001$) was found but also 86% reported a decrease in the nightmares and in the intrusive thoughts.

In a 4-week trial, Berlant (2004) treated 33 civilian patients with chronic PTSD using topiramate (mean: 50 mg/day) as a monotherapy (n=5) or as an adjunctive therapy (n=28). Seventy-seven percent of those who completed the study (n=30) were considered responders (reduction of ≥ 30% in PCL-C scores). At the end of week 4, a significant decline was found in the PCL-C global scores (49%) ($p<0.001$) and in those of the reexperiencing (53%), avoidance/numbing (43%) and hyperarousal (48%) clusters.

2.5 Tiagabine: ***Randomized Clinical Trials:*** In a recent multisite, double-blind, placebo-controlled clinical trial, Davidson *et al.* (2007) assessed the efficacy and tolerability of tiagabine monotherapy (2–16 mg/day; mean: 11.2 mg/day) in the treatment of PTSD. Patients with a history of unresponsiveness to two or more pharmacological trials for PTSD were excluded from the study. Of the 232 participants randomized at baseline, only 141 completed the 12 weeks of treatment. Although tiagabine was well tolerated, it was not significantly superior to placebo, as assessed by the CAPS, DTS, CGI and TOP-8 final scores.

Open Label Studie: Connor *et al.* (2006) assessed the efficacy of tiagabine (mean: 12.5 mg/day) in 26 civilian patients in a two-stage study. In the first phase, an open trial with tiagabine led to a significant decrease in the scores of the SPRINT ($p<0.001$) between baseline and week 12. Next, the 18 patients who had improved during phase 1 were randomized 1:1 to twelve weeks of double-blind treatment, either continuing the tiagabine or switching to placebo. Somewhat surprisingly, both groups fared equally well and maintained the improvement achieved during the first phase.

2.6 Levetiracetam: ***Open Label Studies:*** In a retrospective naturalistic study with 35 civilian patients with chronic refractory PTSD, Kinrys *et al.* (2006) showed that adding levitiracetam (1,000–3,000 mg/day, mean: 1,967 mg/day), a novel anticonvulsant, to antidepressants for 4–20 weeks led to a significant decrease in the scores of the PCL-C.

2.7 Phenytoin: ***Open Label Studies:*** Phenytoin was administered as a monotherapy to 9 combat veterans and civilian patients with PTSD. Blood levels were maintained within the range of 10 to 20 ng/ml for 3 months. At the end of this period, significant reductions in mean total scores of CAPS ($p=0.005$) were noted, as well as in each of its sub-scores ($p<0.05$). Treatment with phenytoin also resulted in social and functional improvement (Bremner *et al.* 2004).

EVIDENCE LEVEL D

2.8 Gabapentin: ***Anecdotal Reports and Case Series:*** Hamner *et al.* (2001) published a retrospective series of 30 cases where gabapentin (300–3,600 mg/day; mean: 1,190 mg/day) was found to be effective as an adjunctive therapy for the treatment of certain PTSD symptoms, such as insomnia and nightmares.

2.9 Vigabatrin: ***Anecdotal Reports and Case Series:*** Macleod (1996) reported 5 cases of PTSD in which vigabatrin (250–500 mg/day) led to a reduction of the exaggerated startle response and to an improvement of the sleep pattern.

3. Adrenergic-inhibiting agents

The increase of the noradrenergic function seen in dangerous situations can lead to the overconsolidation of memories in the amygdala (Deebie and LeDoux 2006; Shin *et al.* 2006). Alpha-1 adrenergic receptor stimulation in CNS disrupts sleep physiology, increases nightmares, enhances the secretion of corticotropin release factor (CRF) – which has anxiogenic properties and disrupts deep sleep – and favors the emergence of primitive alarm-related cognitive processing (Raskind *et al.* 2007). For all these reasons, centrally acting alpha-1 adrenergic receptor antagonists are a promising alternative for the treatment of nightmares, insomnia and other sleep-related PTSD symptoms.

EVIDENCE LEVEL B

3.1 Prazosin: ***Randomized Clinical Trials:*** In an 8-week, placebo-controlled trial, Raskind and colleagues (Raskind *et al.* 2007) compared the efficacy of prazosin (mean: 13 mg/day) and placebo in the treatment of 40 combat veterans with chronic PTSD and intractable nightmares and other sleep disturbances. In twenty cases, prazosin or placebo were added to a pre-existing therapeutic scheme. At the end of the study, patients treated with prazosin showed a significantly greater improvement in the frequency and intensity of trauma-related nightmares (according to the recurrent distressing dreams item of the CAPS), sleep quality (as measured by the *Pittsburgh Sleep Quality Index*, PSQI) (Buysse *et al.* 1989) and overall PTSD symptoms severity (according to the CGI-I). Nevertheless, a comparison of the total CAPS scores failed to show significant differences between the two groups at endpoint. It is noteworthy that prazosin reduced military trauma-related nightmares compared to nightmares of any kind and shifted dream characteristics from those typical of trauma-related nightmares toward those of regular dreams.

Taylor *et al.* (2008) investigated the efficacy of prazosin (2–6 mg/day; mean: 3.1 mg/day) as an augmentation strategy in 11 civilian patients with PTSD and distressing dreams. In this 7-week, classic crossover design study, patients completed random-order three-week long trials of prazosin and of placebo separated by a 1-week washout period. The author found that treatment with prazosin was associated with a greater total sleep time ($p<0.01$), REM sleep

time ($p<0.01$) and mean REM period duration (total REM time per night divided by the number of REM periods per night) ($p<0.05$). The outcome of the PTSD symptoms, measured by the PCL-C and CGI-I, was significantly superior ($p<0.05$) when prazosin was administered instead of placebo.

In a 20-week, double-blind, placebo-controlled crossover RCT, Raskind *et al.* (2003) employed the CAPS and the CGI to measure the therapeutic efficacy of prazosin (mean: 9.5 mg/day) as an augmentation strategy in 10 veterans with chronic refractory PTSD. The authors reported that treatment with prazosin not only decreased the severity of nightmares ($p<0.01$) but also led to reductions in general posttraumatic symptomatology.

Open Label Studies: In a study with a complex methodological design, Taylor *et al.* (2006) studied the role of prazosin as an adjunctive therapy in the treatment of 11 civilian patients with refractory PTSD (6 patients using SSRIs, 6 using non-SSRIs antidepressants, 3 using buspirone and 2 using benzodiazepine or zolpidem). This study was divided in three phases. The first was a one-month open-label trial, where prazosin was used once a day (at night; mean: 3.2 mg/day) and the patients were evaluated with the PCL-C and CGI-S. The doses of prazosin were gradually increased until a reduction of at least 1 point in the item 2 of the PCL-C (repeated, disturbing dreams of a stressful experience) was achieved by 11 patients. At the end of this phase, PCL-C mean score had declined from 67 to 54 ($p<0.01$), while CGI-S average score decreased from 4.1 to 3.2 ($p<0.01$). In the second phase, neuropsychological testing was carried out. In the third phase, ten patients were treated for two weeks with prazosin b.i.d. with the maximum nighttime doses achieved in phase 1. At this point, mean CGI-S scores had dropped from 3.2 to 1.5 ($p<0.01$).

Peskind *et al.* (2003) treated 8 elderly veterans and a Holocaust survivor with chronic PTSD and refractory nightmares with prazosin (2–4 mg/day) for 8 weeks. According to the CGI-I scores, eight patients were moderate to very much improved by the end of the study. Prazosin substantially reduced nightmares as assessed by the specific CAPS item ($p<0.001$).

In a chart review study, Raskind *et al.* (2002) evaluated the use of adjunctive prazosin in 59 combat veterans with refractory PTSD and frequent nightmares. Patients were divided into 3 groups comprised of those who: 1) did not fill their prazosin prescriptions but returned for follow-up (controls, n=8); 2) initiated treatment with prazosin but failed to complete 8 weeks of treatment (n=15); and 3) finished 8 weeks of treatment with prazosin (n=36). For the sake of analysis, groups 2 and 3 were lumped together as those receiving prazosin. Patients were assessed with the CGI-I and with the item of the CAPS covering repeated distressing dreams. Reduction in the nightmares was significantly greater in patients taking prazosin ($p<0.0001$). The mean score of CGI-I as applied to nightmares also revealed a significant improvement in this group.

Anecdotal Reports and Case Series: Daly *et al.* (2005) treated 23 veterans with complaints of nightmares (not necessarily associated with PTSD) with prazosin (1–6 mg/day). In 13 cases, prazosin was used as an adjunctive therapy. After 3 months, nightmares had remitted completely in 20 patients and partially in two.

Taylor and Raskind (2002) used prazosin (1–4 mg/day) as an adjunctive therapy in 5 patients with refractory PTSD. After 6 weeks, all patients attained an at least moderate improvement, according the CGI-I scores for general symptoms and for nightmares. The global score of the CAPS also decreased by at least 20 points in all patients.

EVIDENCE LEVEL C

3.2 Propranolol: ***Open Label Studies:*** In a study with 12 veterans with chronic PTSD (Kolb *et al.* 1984), the administration of propranolol (120–160 mg/day) significantly improved intrusive thoughts, nightmares, insomnia, outbursts of anger, exaggerated startle reaction and hypervigilance.

In a clinical trial with 11 children with acute PTSD secondary to sexual and/or physical abuse (Famularo *et al.* 1988), the use of propranolol at maximum dose of 2.5 mg/kg/day decreased intrusive thoughts and hyperarousal symptoms.

EVIDENCE LEVEL D

3.3 Guanfacine: ***Randomized Clinical Trials:*** Veterans with chronic PTSD who were either medication-free or on a stable therapeutic scheme were randomly assigned to be treated with guanfacine (mean: 2.4 mg/day) (n=29) or with placebo (n=34) for 8 weeks (Neylan *et al.* 2006). Guanfacine showed no effect on PTSD symptoms, subjective sleep quality, or general mood disturbances as measured by the CAPS, the *Impact of Event Scale- Revised* (IES-R) (Weiss and Marmar 1997), the *Hamilton Depression Rating Scale* (Hamilton 1960), the *Symptom Checklist-90 Revised* (SCL-90R) (Derogatis 1977), the *Sleep Quality Index* (Buysse *et al.* 1989) and the *Quality of Life Inventory* (Frisch *et al.* 1992), and was associated with a number of side effects.

3.4 Clonidine: ***Open Label Studies:*** Harmon and Riggs (1996) provided clonidine patches to 7 pre-school children (3 to 6 year-old) with PTSD secondary to abuse and/or neglect. According to the teachers' and the attending physicians' opinion, there was a moderate to marked decrease in aggressiveness in all children and impulsivity, temper outbursts, emotional lability, hyperarousal, hypervigilance, generalized anxiety, oppositional behavior, insomnia or nightmares improved in 71% of the sample.

4. Opioid antagonists

Studies demonstrating increased central opioid activity in individuals with PTSD (van der Kolk *et al.* 1989) provided a rationale for preliminary trials of opioid antagonists in the treatment of PTSD symptoms, mainly numbing and avoidance. So far, however, results have been inconclusive.

EVIDENCE LEVEL D

4.1 Nalmefene: ***Open Label Studies:*** Glover (1993) administered nalmefene, a non-FDA approved oral opioid antagonist, to 18 combat veterans with chronic PTSD. Eight patients reported improvement at higher doses and showed a marked decrease of emotional numbing and of other PTSD symptoms, such as exaggerated startle response, flashbacks, nightmares, intrusive thoughts and rage attacks.

Naltrexone: ***Open Label Studies:*** Lubin *et al.* (2002) treated 8 patients with chronic PTSD with naltrexone (100–200 mg/day) for two weeks with disappointing results. Only clinically insignificant improvements in intrusive and hyperarousal symptoms were observed in the seven patients who completed the trial. All patients reported early side effects that severely curtailed the efforts to achieve higher doses.

5. Benzodiazepines

Benzodiazepines enhance GABAergic transmission and exert a inhibitory effect on the amygdala, a brain structure that is known to be involved in the processing of fear (Davis and Myers 2002). Given that PTSD shares many of its symptoms with the anxiety disorders and

that benzodiazepines are efficacious in the treatment of the latter (Hoffman and Mathew 2008), there is rationale for using this class of drugs in the prevention and treatment of PTSD.

EVIDENCE LEVEL D

5.1 Alprazolam: ***Randomized Clinical Trials:*** In a 12-week crossover study, Braun *et al.* (1990) treated 16 patients suffering from chronic PTSD with alprazolam (1.5–6 mg/day) or placebo for 5 weeks, with a 2-week washout period in between. Although anxiety symptoms were significantly alleviated by treatment with alprazolam, no difference involving the PTSD symptoms *per se* were reported, as assessed by IES.

Open Label Studies: Gelpin *et al.* (1996) treated 13 victims of very recent accidents or terrorist attacks (range of 2–18 days after the traumatic event; mean: 6.7) with either clonazepam (mean: 2.7 mg/day) or alprazolam (2.5 mg/day) and compared them with 13 matched trauma survivors who were treated as usual (i.e. received no benzodiazepines). After 6 months, the benzodiazepine group did not differ from the controls in IES and *Mississippi Rating Scale for Combat-Related PTSD-civilian trauma version* scores. Furthermore, 9 individuals from the benzodiazepine group and 3 controls were found to meet diagnostic criteria for PTSD according to the CAPS.

5.2 Temazepam: ***Open Label Studies:*** In a non-blinded trial, Mellman and colleagues (2002) randomized 21 victims of recent civilian trauma (mean: 14 days) who were manifesting PTSD symptoms to a 7-day course of temazepam (30 mg/day for 5 days followed by 15 mg/day for 2 day) or placebo. After six weeks, 55% of the subjects who were treated with temazepam and 27% of those who received placebo met diagnostic criteria for PTSD, according to the CAPS. Although treatment with temazepam led to sleep improvement, this positive effect did not persist after drug discontinuation.

6. Others

EVIDENCE LEVEL D

6.1 Cyproheptadine: Cyproheptadine is an antihistaminic medication that blocks $5HT_{2A}$ auto-receptors. Given that H_1 antagonism produces sedation and $5HT_{2A}$ blockade enhances serotonergic activity, antihistaminic drugs are considered a potentially useful pharmacological approach to the treatment of PTSD.

Open Label Studies: Clark *et al.* (1999a) medicated 16 patients with PTSD with cyproheptadine (4–8 mg/day) during a week. They used the Miami Veterans Administration Medical Center (VAMC) Post-Sleep Questionnaire to evaluate shifts in sleep patterns and the frequency of nightmares. However, cyproheptadine failed to show any consistent benefit and was poorly tolerated by patients.

6.2 Dehydroepiandrosterone (DHEA): It is well-known that cortisol can induce neuronal damage, particularly hyppocampal atrophy (Sapolsky 2000). Dehydroepiandrosterone is an endogenous anti-glucocorticoid that protects neurons from the neurotoxic effects of cortisol (Kalimi *et al.* 1994; Kaminska *et al.* 2000). A recent study have reported a negative correlation between DHEA plasmatic levels and PTSD symptoms, i.e., the higher the DHEA levels, the lower the severity of the symptoms in individuals with PTSD (Rasmusson *et al.* 2004).

Open Label Studies: Sangeman *et al.* (Sageman and Brown 2006) reported having used DHEA-S (dehydroepiandrosterone sulfate, 25–100 mg/day) to treat 5 women with severe chronic PTSD resulting from early life physical/sexual abuse. The participants were highly symptomatic despite having undergone extensive psychotherapy and years of

pharmacotherapy. This trial led to decreases in dissociation, avoidance, numbing, reexperiencing, hyperarousal, anger, affective instability, and insomnia symptoms and an improvement in libido. Although preliminary in nature, these results are encouraging, particularly considering the severity and chronicity of PTSD in these patients.

6.3 Lithium carbonate: Several studies reported the efficacy of lithium in reducing aggression and impulsivity (Craft *et al.* 1987; Lewis 2000; Tyrer *et al.* 1984; Forster *et al.* 1995). As these symptoms are frequently found in PTSD, it has been proposed that lithium might be useful in the treatment of this condition.

Open Label Studies: Kitchner and Greenstein (1985) used lithium (300–600 mg/day) to treat 5 veterans with refractory PTSD. Four patients reported improvements in anxiety, irritability, rage and insomnia. The fifth patient improved only when propranolol (10 mg/day) was added to augment lithium.

DISCUSSION

Antidepressants are considered the primary class of medications for the treatment of PTSD. Given that several RCTs have repeatedly demonstrated their efficacy (Brady *et al.* 2000; Connor *et al.* 1999; Davidson *et al.* 2001; Marshall *et al.* 2001a; Neylan *et al.* 2001; Tucker *et al.* 2001; van der Kolk *et al.* 1994), it is now well established that SSRIs are the first-line pharmacotherapy for PTSD (Ursano *et al.* 2004). Further options include the dual action selective serotonin and noradrenaline reuptake inhibitors, tricyclics, monoaminoxidase inhibitors and others (nefazodone, bupropion etc.). The limited number of RCTs assessing alternative medications to be employed when patients do not tolerate or not respond to antidepressants poses a challenge to the clinicians. The authors of the present review decided not to limit the present systematic review to RCTs since open trials and case series are often the first evidence supporting innovative treatment (Albrecht *et al.* 2005). Indeed, clinicians in their daily practice frequently have no controlled clinical trial-based evidence to guide them through the decision-making process and have to rely on the best available piece of evidence. Given that the majority of the studies reviewed here suffered from methodological shortcomings, there is currently no medication for the treatment of PTSD within the level A of evidence other than antidepressants. Level B of evidence was achieved by risperidone, olanzapine, lamotrigine, valproate and prazosin. Seven medications warranted level C and 13 level D (Table 1).

In four out of six RCTs with risperidone, this medication was shown to be superior to placebo in reducting overall PTSD severity (Bartzokis *et al.* 2005; Monnelly *et al.* 2003; Padala *et al.* 2006; Reich *et al.* 2004). Only Hamner *et al.* (2003b) and Rothbaum *et al.* (2008) failed to find significant differences. It must be noted, however, that the sample investigated by Hamner and his collaborators was composed exclusively by war veterans, a population that is characterized by high levels of refractoriness (Mohamed and Rosenheck 2008) and that their study duration (5 weeks) was the shortest of all the five RCTs while Rothbaum and colleagues' study was conducted with a small number of patients refractory to first-line treatment with sertraline. It is also worth mentioning that none of these six RCTs have demonstrated the efficacy of risperidone on the symptoms of the avoidance/numbing cluster.

As noted above, the two existing RCTs on olanzapine in PTSD produce conflicting results: while Stein *et al.* (2002) found that olanzapine was superior to placebo as an augmentation therapy in the treatment of 19 male war veterans with refractory PTSD, Butterfield *et al.* (2001) found no advantage for olanzapine in a sample of 15 civilian PTSD patients (14 women, with 4 drop-outs during the study). The inconsistency of the results could be ascribed to several factors including differences in treatment strategies (augmentation *vs.* monotherapy),

demographic make-up of the sample, type of trauma, level of treatment resistance, and time elapsed since the traumatic event.

It must be kept in mind that the efficacy of the antipsychotics in the treatment of refractory PTSD may not reflect any specific action on posttraumatic symptoms, but rather their effects on non-specific symptoms, such as insomnia, nightmares, and associated psychotic ideation. It is also important to note that since these trials were essentially short-term ones, the possibility of the occurrence of severe side effects such as metabolic syndrome and tardive dyskinesia should remain a major concern.

Although anticonvulsants have assumed an ever increasing role in the psychiatric armamentarium, being now used regularly to treat mood (Carvalho *et al.* 2007) and anxiety disorders (Mula *et al.* 2007), their real worth in the treatment of post-traumatic stress remains uncertain. Studies on the efficacy of anticonvulsants in PTSD far outnumber those of antipsychotics, but the former are clearly methodologically inferior to the latter. Only six RCTs were conducted with anticonvulsants. Most studies described a decrease in the severity PTSD symptoms after anticonvulsants were added to a pre-existing therapeutic scheme as an augmentation strategy. Herzberg *et al.* (1999) reported that lamotrigine as a monotherapy was effective in reducing general symptoms, reexperiencing and avoidance/numbing, but not hyperarousal, in treatment-refractory PTSD. Steiner *et al.* (2007) demonstrated that divalproex sodium, especially at doses between 500–1,500 mg/day, could ameliorate PTSD symptoms. It should be noted that this study did not compare the use of divalproate against that of placebo. However, in a placebo-controled, double-blind study, Davis *et al.* (2008) found that divalproex had no discernible effects on the chronic PTSD symptoms of veterans, even in high doses. Tucker *et al.* (2007) reported the effectiveness of topiramate as a monotherapy in ameliorating symptoms of reexperiencing (but not the global scores of PTSD). These findings were replicated by Lindley *et al.* (2007), who used topiramate as an augmentation strategy. Davidson *et al.* (2007) failed to demonstrate the superiority of tiagabine over placebo in the treatment of 232 civilian patients with PTSD, as determined by four differents outcomes measures, even after excluding patients with history of unresponsiviness to PTSD treatment.

Prazosin, an adrenergic-inhibiting agent, is a promising alternative in the treatment of PTSD, particularly when trauma-related nightmares and sleep disturbances are prominent symptoms, as shown by three recent RCTs. Taylor *et al.* (2008) found that prazosin not only improved the physiological patterns of sleep and produced positive qualitative changes in the character of pathological dreams, but also reduced overall PTSD severity, as measured by PCL-C. Raskind *et al.* (2007) showed a significant reduction in nightmares (through the distressing dreams item of the CAPS), improvement of sleep quality (as measured by the PSQI) and decrease of the severity of PTSD symptoms (assessed through the CGI-I) in veterans medicated with prazosin, as compared to those treated with placebo. Nevertheless, no significant differences were found in CAPS total scores. Finally, Raskind *et al.* (2003) reported that prazosin was effective for treating symptoms of the re-experiencing, avoidance/numbing, and hyperarousal clusters in treatment-resistant PTSD. Other adrenergic-inhibiting agents such as propranolol and clonidine were not yet evaluated by RCTs, but the few open-label studies published so far suggest that these drugs can alleviate some sleep disturbances (i.e. nightmares) and especially hyperarousal symptoms. A recent RCT showed that guanfacine (either as an augmentation strategy or as monotherapy) was ineffective in the treatment of PTSD symptoms (Neylan *et al.* 2006).

Benzodiazepines are frequently prescribed by physicians in the aftermath of a traumatic event in an effort to prevent the development of psychological sequelae or, if PTSD eventually arises, to reduce active post-traumatic symptoms, like hypervigilance, or control associated non-specific behavioral disturbances, such as marked anxiety or agitation.

Thus far, there is no compelling scientific evidence of the effectiveness of benzodiazepines either in the prevention of PTSD or in the treatment of its core symptoms although clinical experience suggests that they may improve sleep and agitation, at least in the short term. These limited advantages must be weighted against the marked potential for addiction that characterizes this class of drugs, particularly considering that PTSD patients have higher rates of drug abuse/dependence than the general population (Kessler *et al.* 1995). Recently, Westra *et al*. (2004) have reported that individuals with anxiety disorders who take benzodiazepines exhibit a reduced capacity to remember material presented in cognitive-behavioral therapy and hypothesized that this memory impairment may account for the lower efficacy of this modality of psychotherapy in these patients (Westra *et al*., 2004). In addition, a few studies suggest that benzodiazepines may contribute to the development and/or chronification of posttraumatic symptoms (Gelpin *et al.* 1996; Mellman *et al.* 2002). Following the fundamental principle of Medicine, "*primum non nocere*", future RCTs should further investigate the potentially iatrogenic effects of benzodiazepines before they can be safely recommended for the treatment of PTSD.

The scientific evidence supporting the use of opioids antagonists in PTSD is still limited: two existing open-label trials showed disappointing results (Glover 1993; Lubin *et al.* 2002).

Altough the use of cyproheptadine in the treatment of PTSD has a good rationale, the only open-label trial available found low efficacy and a high rate of adverse effects. Others drugs, such as dehydroepiandrosterone and propranolol, may eventually turn out to be clinically useful, but for now the few existing studies suffer from methodological limitations.

The studies reviewed here must be taken with caution for several reasons. First, many of these studies failed to specify whether the medications were employed as a monotherapy or as an augmentation strategy. This is a serious methodological problem that not only jeopardizes the comparability of the studies, but also limits their clinical usefulness. Second, the majority of the case reports and open label trials reported positive results with several medications that had not yet been otherwise rigorously evaluated in the this context. A publication bias could explain the predominance of favorable results in this literature, given that editors and authors tend to favor positive findings. Third, the majority of these studies were carried out with combat veterans, a population that is notoriously refractory to conventional treatment, making the results difficult to extrapolate to civilian samples. Fourth, the criteria for therapeutic response currently adopted are based on partial improvement rather than on full remission and may overestimate the clinical significance of even modest symptomatic improvement in PTSD. For instance, when the definition of clinical response adopted is a reduction $\geq 30\%$ in CAPS scores, it is likely that many patients considered to be responders are continuing to suffer from clinically relevant subsyndromal PTSD, a condition that is known to be associated with substantial impairment (Marshall *et al.* 2001b). Finally, the system of classification of the level of scientific evidence used in this review did not take into consideration the number of participants in the studies.

CONCLUSIONS

The well-known difficulties in managing PTSD are aggravated when the patient does not respond to or do not tolerate treatment with antidepressants. Our review of the literature suggested that, in these cases, there are a few alternatives to be considered. Risperidone is the medication with the strongest empirical support for a role as an alternative treatment of PTSD, particularly as an augmentation strategy, despite not having its efficacy demonstrated on avoidance and emotional numbing symptoms. Given its safety profile, risperidone can be envisaged as an effective add-on therapy in cases where patients could not reap full benefits from the treatment with SSRIs.

Another promising medication is prazosin, particularly in cases where trauma-related nightmares and insomnia are prominent complaints. This finding highlights the facts that symptoms of PTSD are heterogeneous and each of them may respond differently to specific medication and provides a strong stimulus for investigating new symptom-specific drugs. Unfortunately, the symptom cluster that is associated with more severe functional impairment - avoidance/numbing - is the one that is less responsive to available alternative pharmacotherapic agents.

On a negative note, it was surprising to find that one of the most deeply entrenched habits of clinicians, that of treating acutely traumatized patients with benzodiazepines in an attempt to minimize putative psychological sequelae, not only lacks empirical support but may also have the opposite effect. Efforts should be made to educate clinicians about the proper management of acute psychological trauma.

It must be emphasized that the choice of a medication should take into consideration not only the nature and the severity of the posttraumatic symptoms, but also the existence of associated comorbidities, the history of previous treatment trials, the possibility of drug interactions, the occurrence of side effects, and the physical and psychological conditions of the patient. Hopefully, future controlled randomized trials with newer drugs will be able to address many of the uncertainties that plague current knowledge about the treatment of PTSD and teach us innovative ways to reduce the suffering and the disability associated with this disorder.

ABBREVIATIONS

AP, Atypical Antipsychotics
b.i.d, bis in die or twice a day
BPRS, Brief Psychiatric Rating Scale
CAPS, Clinician Administered Posttraumatic Stress Disorder Scale
CGI, Clinical Global Impression
CGI-I, Clinical Global Impressions scale - Improvement item
CGI-S, Clinical Global Impressions - Severity of Illness Scale
CNS, Central Nervous System
CRF, Corticotropin Release Factor
DGRP, Physician Administered Duke Global Rating for PTSD Scale
DHEA, Dehydroepiandrosterone
DHEA-S, dehydroepiandrosterone sulfate
DTS, Davidson Trauma Scale
ER, Extended Release
FDA, Food and Drug Administration
GABA, Gamma-Aminobutyric Acid
IES-R, Impact of Event Scale- Revised
mg, Milligram
mg/kg/day, Milligram per Kilogram per Day
ng/ml, Nanograms per Millilitre
PANSS, The Positive and Negative Symptoms Scale
PCL-C, Posttraumatic Checklist - Civilian Version
PGI-I, Patient Global Impression - Improvement scale
PSS-SR, Posttraumatic Stress Disorder Symptoms Scale–Self Report
PTSD, Posttraumatic Stress Disorder
PTSD-I, Posttraumatic Stress Disorder Interview
PSQI, Pittsburgh Sleep Quality Index
RCTs, Randomized Clinical Trials
REM, Rapid Eye Movement

SCL-90R, Symptom Checklist-90 Revised
SNRI, Serotonin-norepinephrine Reuptake Inhibitor
SPRINT, Short PTSD Rating Interview
SSRIs, Selective Serotonin Reuptake Inhibitors
TOP-8, Treatment Outcomes PTSD Scale
TSCC, Traumatic Symptom Checklist in Children
VAMC, Miami Veterans Administration Medical Center

ACKNOWLEDGMENTS

This research was supported in part by CNPq (Nacional Research Council) – Federal Government of Brazil and Grant R01-MH056350-06 from the National Institute of Mental Health. The authors thank the anonymous reviewers for the invaluable comments and suggestions.

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Table 1

Number of articles with non-antidepressant agents on the treatment of PTSD classified according to its experimental design and evidence level.

Drug	RCTs	Open-label studies	Case reports and series	Total	Evidence level
Atypical antipsychotics:					
Risperidone	6	3	0	9	B
Olanzapine	2	2	2	6	B
Quetiapine	0	4	1	5	C
Clozapine	0	1	0	1	D
Aripiprazole	0	0	1	1	D
Anticonvulsants:					
Valproic acid	2	5	0	7	B
Lamotrigine	1	0	0	1	B
Topiramate	2	2	0	4	C
Tiagabine	1	1	0	2	C
Carbamazepine	0	3	0	3	C
Levetiracetam	0	1	0	1	C
Phenytoin	0	1	0	1	C
Gabapentin	0	0	1	1	D
Vigabatrin	0	0	1	1	D
Adrenergic-inhibiting agents:					
Prazosin	3	3	2	8	B
Propranolol	0	2	0	2	C
Guanfacin	1	0	0	1	D
Clonidine	0	1	0	1	D
Opioid antagonists:					
Nalmefene	0	1	0	1	D
Naltrexone	0	1	0	1	D
Benzodiazepines:					
Alprazolam	1	1	0	2	D
Temazepam	0	1	0	1	D
Others:					

Drug	RCTs	Open-label studies	Case reports and series	Total	Evidence level
Cyproheptadine	0	1	0	1	D
Dehydroepiandrosterone	0	1	0	1	D
Lithium	0	1	0	1	D

RCTs: randomized clinical trials.

Evidence level: B) At least one positive randomized clinical trial (in addition to level C evidence); C) Positive open trials, anecdotal evidence and case series, as well as endorsement by some experts; D) Positive anecdotal reports but not highly endorsed by expert panels.

Prog Neuropsychopharmacol Biol Psychiatry. Author manuscript; available in PMC 2010 March 17.

Table 2

Summary of randomized controlled trials for pharmacologic alternatives to antidepressants for treatment of PTSD.

Study (year)	Sample (N)	Drug (mg/day)	Monotherapy / augmentation	Duration (weeks)	Outcome Measures	Was active drug superior to placebo? (p-value)*			
						Symptoms of PTSD	Cluster B	Cluster C	Cluster D
Atypical antipsychotics									
Bartzokis *et al.* (2005)	Veterans (65)	Risperidone (1 to 3)	Augmentation	16	CAPS	Yes (< .05)	No	No	Yes (< .01)
Hamner *et al.* (2003)	Veterans (37)	Risperidone (1 to 6)	Augmentation	5	CAPS	No	No	No	No
Reich *et al.* (2004)	Civilians (21)	Risperidone (0.5 to 8)	Augmentation	8	CAPS	No	No	No	No
					CAPS-2	Yes (.015)	Yes (< .001)	No	Yes (.006)
Padala *et al.* (2006)	Civilians (20)	Risperidone (1 to 6)	Monotherapy	12	CAPS	Yes (.04)	NR	NR	NR
					TOP-8	Yes (.028)	NR	NR	NR
Rothbaum et al. (2008)	Civilians (20)	Risperidone (mean: 2.1)	Augmentation	8	CAPS	No	NR	NR	NR
					CGI	No	NR	NR	NR
					DTS	No	Yes, insomnia (.03)	NR	NR
Monnelly *et al.* (2003)	Veterans (15)	Risperidone (0.5 to 2)	Augmentation	6	PCL-M	Yes (.02)	Yes (.001)	No	No
Stein *et al.* (2002)	Veterans (19)	Olanzapine (10 to 20)	Augmentation	8	CAPS	Yes (> .05)	NR	NR	NR
					CGI	No	NR	NR	NR
					PSQI (nightmares)	NA	Yes (.01)	NA	NA
Butterfield *et al.* (2001)	Civilians (15)	Olanzapine (5 to 20)	Monotherapy	10	TOP-8	No	No	No	No
					SPRINT	No	No	No	No
Anticonvulsants									

Study (year)	Sample (N)	Drug (mg/day)	Monotherapy / augmentation	Duration (weeks)	Outcome Measures	Was active drug superior to placebo? (p-value)*			
						Symptoms of PTSD	Cluster B	Cluster C	Cluster D
Davis et al. (2008)	Veterans (82)	Divalproex (mean: 2,309)	Monotherapy	8	CAPS	No	No	No	No
					CGI	No	NR	NR	NR
					DTS	No	NR	NR	NR
					TOP-8	No	NR	NR	NR
Tucker *et al.* (2007)	Civilians (38)	Topiramate (25 to 400)	Monotherapy	12	CAPS	No	Yes (.038)	No	No
					DTS	No	No	No	No
					TOP-8	Yes (.025)	No	No	No
					CGI	No	NR	NR	NR
Lindley *et al* (2008)	Veterans (24)	Topiramate (50 to 200)	Augmentation	7	CAPS	No	Yes (< .05)	No	No
					CGI	No	NR	NR	NR
					PGI-I	No	NR	NR	NR
Davidson *et al* (2007)	Civilians (232)	Tiagabine (2 to 16)	Monotherapy	12	CAPS	No	NR	NR	NR
					DTS	No	NR	NR	NR
					TOP-8	No	NR	NR	NR
					CGI	No	NR	NR	NR
Hertzberg *et al.* (1999)	Civilians and veterans (15)	Lamotrigine (50 to 500)	Monotherapy	12	DGRP	Yes	Yes	Yes	No
Adrenergic-inhibiting agents									
Neylan *et al.* (2006)	Veterans (63)	Guanfacin (1 to 3)	Augmentation	8	CAPS	No	No	No	No
					IES-R	No	No	No	No
					SQI	No	No	No	No
Raskind *et al* (2007)	Veterans (40)	Prazosin (mean: 13)	Augmentation	8	CAPS	No	Yes, nightmares (.02)	NR	NR
					PSQI	NA	Yes (.008)	NR	NR

Study (year)	Sample (N)	Drug (mg/day)	Monotherapy / augmentation	Duration (weeks)	Outcome Measures	Was active drug superior to placebo? (p-value)*			
						Symptoms of PTSD	Cluster B	Cluster C	Cluster D
					CGI	Yes (.002)	NR	NR	NR
Taylor et. al. (2008)	Civilians (13)	Prazosin (2 to 6)	Augmentation	7 (*crossover* at week 3)	PCL-C	Yes (< .05)	NR	NR	NR
					CGI	Yes (< .05)	NR	NR	NR
Raskind et al. (2003)	Veterans (10)	Prazosin (mean: 9.5)	Augmentation	20 (*crossover* at week 10)	CAPS	Yes (< .01)	Yes (< .001)	Yes (< .001)	Yes (< .001)
					Yes (< .01)	Yes	Yes	Yes	
Benzodiazepines									
Braun *et al.* (1990)	Civilians and veterans (16)	Alprazolam (1.5 to 6)	Monotherapy	12 (crossover at week 5)	IES	No	No	No	NA

*When not reported, or no statistical significant difference was found, or was not reported by the authors.

Cluster B: reexperiencing; cluster C: avoidance/numbing; Cluster D: hyperarousal.

CAPS: Clinician-Administered PTSD Scale; CAPS-2: Clinician-Administered PTSD Scale, 1 week version; CGI: Clinical Global Impression; DGRP: Duke Global Rating for PTSD scale; DTS: Davidson Trauma Scale; IES-R: Impact Event Scale Revised; NA: not applicable; NR: not reported; PCL-M: Posttraumatic Stress Disorder Checklist Military version; PGI-I: Patient Global Impression – Improvement scale; PSQI: Pittsburgh Sleep Quality Index; SPRINT: Short PTSD Rating Interview; SQI: Subjective sleep quality; TOP-8: Treatment Outcomes PTSD Scale.

Medical Marijuana: Effective Harm Reduction Strategy

We are the Drug Policy Alliance.

October 2012

Overview of State Medical Marijuana Laws

Seventeen states – Alaska,[1] Arizona,[2] California,[3] Colorado,[4] Connecticut ,[5] Delaware,[6] Hawaii,[7] Maine,[8] Michigan,[9] Montana,[10] Nevada,[11] New Jersey,[12] New Mexico,[13] Oregon,[14] Rhode Island,[15] Vermont[16] and Washington[17] – and the District of Columbia[18] currently provide legal protection under state law for seriously ill patients whose doctors recommend the medical use of marijuana. Some 90 million Americans, or roughly 29 percent of the U.S. population, currently reside in a state where marijuana is legal for medical purposes. These effective medical marijuana laws have been passed by both ballot initiatives and by state legislatures.[19]

Three states allow PTSD to be a qualifying condition: New Mexico; Deleware and California.

By enacting medical marijuana laws, states have succeeded in:

- Helping over a million seriously ill people who need marijuana to relieve pain or treat medical conditions, such as cancer, PTSD, chronic pain, HIV/AIDS and multiple sclerosis;[20]
- Providing almost complete protection from arrest to patients who use marijuana, since 99 percent of all marijuana arrests occur at the state and local levels;
- Raising millions of dollars in revenue for the state through new taxes.[21] The value of the medical marijuana industry nationwide is currently estimated at $1.7 billion and forecast to reach almost $9 billion within five years.[22]

Medical Marijuana is Legal in 17 States & D.C.

Impact of Medical Marijuana Laws

A recent article confirmed that medical marijuana does not lead to increased marijuana use. The researchers found, "Difference-in-differences estimates suggested that passing MMLs (medical marijuana laws) decreased past-month use among adolescents ... and had no discernible effect on the perceived riskiness of monthly use. ... [These] estimates suggest that reported adolescent marijuana use may actually decrease following the passing of medical marijuana laws."[23] They concluded, "We find limited evidence of causal effects of medical marijuana laws on measures of reported marijuana use."[24] Another recent article concluded likewise, writing: ""Our results suggest that the legalization of medical marijuana was not accompanied by increases in the use of marijuana or other substances such as alcohol and cocaine among high school students. Interestingly, several of our estimates suggest that marijuana use actually declined

with the passage of medical marijuana laws." [25]
An in-depth 2007 analysis reported similar findings: "[C]onsistent with other studies of the liberalization of cannabis laws, medical cannabis laws do not appear to increase use of the drug." [26] And another investigation into the impact of Rhode Island's medical marijuana law on marijuana consumption presented their research at the American Public Health Association annual conference, reported, "Our study did not find increases in adolescent marijuana use related to Rhode Island's 2006 legalization of medical marijuana,"[27]

Like any doctor-recommended or prescribed medication, patients should *never* drive a car or operate heavy machinery while under the influence of such medication.[28] Medical marijuana laws have not been associated with any increase whatsoever in traffic fatalities. In fact, the opposite effect may have taken place; the only study to-date investigating the impact of medical marijuana laws on traffic deaths found that "legalization is associated with a nearly 9 percent *decrease* in traffic fatalities, most likely to due to its impact on alcohol consumption."[29] The same study also found no increase in youth use of marijuana in states where it has been legalized for medical purposes.

Not only has the scientific community confirmed marijuana's medicinal benefits, but it has also concluded that marijuana has a wide margin of safety as a medicine, meaning that it typically poses fewer risks to patient health and well-being than many conventionally-prescribed treatments.[30] A recent study published in the United Kingdom's prestigious medical journal, *The Lancet*, ranked the relative harms of legal and illegal substances – and listed marijuana below many common legal drugs and medications.[31] Reports by the IOM, World Health Organization, and other well-regarded scientific and medical institutions have demonstrated that marijuana, by contrast, is unlikely to produce physiological dependence, and there is no amount of marijuana that can result in an overdose.[32] In the words of the IOM, "the acute side-effects of marijuana use are within the risks tolerated for many medications."[33] And according to the WHO, "There are no recorded cases of overdose fatalities attributed to cannabis, and the estimated lethal dose for humans extrapolated from animal studies is so high that it cannot be achieved by recreational users.[34]

The scientific literature does not support a causal link between marijuana and other drug use.[35] Marijuana is not a "gateway drug."[36] As the IOM stated over a decade ago, "There is no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit drugs."[37]

A recent study also concluded that many other factors besides marijuana use, such as stress and unemployment, are determinative of whether a young person uses hard drugs or not.[38] Most marijuana users never try, let alone become addicted, to harder drugs. Regarding the potential for marijuana dependence or abuse, the IOM concluded, "few marijuana users become dependent on it . . . and marijuana dependence appears to be less severe than dependence on other drugs."[39] These findings are identical to those of a 2010 Global Commission of experts that reviewed marijuana's potential for dependence and other harms.[40] One of the Commission's main conclusions: "From a public health perspective, the harms associated with cannabis are modest when compared to legal drugs (alcohol and tobacco) and illegal drugs (amphetamines, heroin and cocaine)."[41]

In fact, **new research suggests that marijuana may aid some in recovery from addictions to alcohol and other drugs.** Confirming earlier findings, one recent study of medical marijuana patients found that some "have been engaging in substitution by using [marijuana] as an alternative to alcohol, prescription and illicit drugs."[42] The top two reasons listed by participants as reasons for substituting marijuana were "less adverse side effects" (65 percent) and "better symptom management." (57.4 percent). A newly published survey of applicants for the medical use of marijuana in California conducted by RAND Corporation similarly found that "half of the applicants reported using marijuana as a substitute for prescription drugs."[43]

More recently –and more promisingly—a group of researchers estimated the effect of medical marijuana laws on suicide rates. Their analysis revealed that "the passage of a **medical marijuana law is associated with an almost 5 percent reduction in the total suicide rate, an 11 percent reduction in the suicide rate of 20- through 29-year-old males, and a 9 percent reduction in the suicide rate of 30- through 39-year-old males."**[44]

Inhaled marijuana has also been found to complement prescription opioid pain medicines well, enhancing the efficacy of (and safely interacting with) these more powerful narcotic medications. An important recent study reported that their subjects' pain "was significantly decreased after the addition of vaporized cannabis", and suggested that **cannabis treatment "may allow for opioid treatment at lower doses with fewer [patient] side effects."**

The authors concluded that their results "demonstrate that inhaled cannabis safely augments the analgesic effects of opioids."[45]

"Prescribing cannabis in place of opioids for neuropathic pain may reduce the morbidity and mortality rates associated with prescription pain medications and may be an effective harm reduction strategy."[46]

National, International and State Organizations that Support Medical Marijuana Access or Research

Highly regarded medical organizations and associations, such as the American College of Physicians, American Nurses Association, American Public Health Association, British Medical Association, Canadian Medical Association, Leukemia and Lymphoma Society, AIDS Action Council, American Academy of HIV Medicine, Lymphoma Foundation of America , and the state medical associations of New York, California and Rhode Island, have either acknowledged the promise of marijuana as a medicine or provided an outright endorsement of it.[47]

In 2009, the American Medical Association adopted a resolution calling for the government to review its classification of marijuana, in order to allow more research into the medicinal uses of marijuana.[48]

Below is a fuller, but not exhaustive, list of organizations that support immediate access to medical marijuana, followed by organizations that support expanding federal research into marijuana's therapeutic potential.[49]

Organizations Supporting Immediate Legal Access to Medical Marijuana

International and National Organizations
AIDS Action Council
AIDS Treatment News
American Academy of Family Physicians
American Bar Association
American Medical Student Association
American Medical Women's Association
American Nurses Association
American Preventive Medical Association
American Public Health Association
Arthritis Research Campaign (United Kingdom)
Australian Medical Association (New South Wales) Limited
Australian National Task Force on Cannabis
Belgian Ministry of Health
British House of Lords Select Committee on Science and Technology
British House of Lords Select Committee On Science and Technology (Second Report)
British Medical Association
Canadian AIDS Society
Canadian Special Senate Committee on Illegal Drugs
French Ministry of Health
Health Canada
Kaiser Permanente
Lymphoma Foundation of America
The Montel Williams MS Foundation
Multiple Sclerosis Society (Canada)
The Multiple Sclerosis Society (United Kingdom)
National Academy of Sciences Institute Of Medicine (IOM)
National Association of People with AIDS
National Association for Public Health Policy
National Women's Health Network
National Latino Congreso, which includes:
The League of United Latin American Citizens (LULAC)
William C. Velasquez Institute
National Alliance of Latin American and Caribbean Communities (NALACC)
Mexican-American Legal Defense and Education Fund
Hispanic Federation, and
Mexican American Political Association (MAPA)
National Nurses Society on Addictions
National Latina/o Lesbian, Gay, Bisexual And Transgender Association
National Native American AIDS Prevention Center
Netherlands Ministry of Health

New England Journal of Medicine
New South Wales (Australia) Parliamentary Working Party on the Use of Cannabis for Medical Purposes

Health Organizations Supporting Medical Marijuana Research

American Cancer Society
American College of Physicians
American Medical Association
American Osteopathic Association
American Society of Addiction Medicine
British Medical Journal
California Medical Association
California Society on Addiction Medicine
Congress of Nursing Practice
Gay and Lesbian Medical Association
National Institutes of Health (NIH) Workshop on the Medical Utility of Marijuana
Texas Medical Association
Vermont Medical Society
Wisconsin State Medical Society

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[1] Alaska Stat. §17.37 (2008). For more information, visit Alaska Department of Health and Social Services, Bureau of Vital Statistics: http://www.hss.state.ak.us/dph/bvs/marijuana.htm.
[2] Proposition 203 (2010). For more information, visit Arizona Department of Health Services: http://www.azdhs.gov/prop203/.
[3] Cal. Health & Safety Code §§ 11362.5, 11362.7 – 11362.83 (2009). For more information, visit California Department of Public Health: http://www.cdph.ca.gov/programs/mmp/pages/medical%20marijuana%20program.aspx.
[4] Colo. Rev. Stat. §§ 12-43.3-101–12-43.3-106 (2010). For more information, visit Colorado Department of Public Health & Environment: http://www.cdphe.state.co.us/hs/medicalmarijuana/index.html.
[5] Connecticut: Public Act 12-55, An Act Concerning the Palliative Use of Marijuana.
[6] 78 Del. Laws, c. 23, § 1;, Del. Code Title 16 §§ 4901A-4926A. Regulated by Delaware Department of Health and Social Services.
[7] Haw. Rev. Stat. §§ 329.121 – 329.128 (2010). For more information, visit Hawaii Department of Public Safety: http://hawaii.gov/psd/law-enforcement/narcotics-enforcement/Patient%20Information%20for%20the%20authorized%20medical%20use.pdf/view.
[8] Me. Rev. Stat. Ann. tit. 22 §§ 2421–2430-A (2010). For more information, visit Maine Department of Health and Human Services: http://www.maine.gov/dhhs/mmma/index.shtml
[9] Mich. Comp. Laws §§ 333.26421–333.26430 (2010). For more information, visit Michigan Bureau of Health Professions at the Michigan Department of Licensing and Regulatory Affairs: www.michigan.gov/mmp.
[10] Mont. Code Ann. § 50-46 (2009). For more information, visit Montana Department of Public Health & Human Services: http://www.dphhs.mt.gov/marijuanaprogram/.
[11] Nev. Rev. Stat. § 453A (2010); Nev. Admin. Code § 453A (2010). For more information, visit Nevada Department of Health and Human Services: http://health.nv.gov/medicalmarijuana.htm
[12] N.J. Rev. Stat. § 24:6I (2010). For more information, visit New Jersey Department of Health: http://www.state.nj.us/health/med_marijuana.shtml
[13] N.M. stat. § 26-2B (2010). For more information, visit New Mexico Department of Health: http://www.health.state.nm.us/idb/medical_cannabis.shtml.
[14] Or. Rev. Stat. § 475.300–346 (2009). For more information, visit Oregon Department of Human Services, Public Health Division: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/medicalmarijuanaprogram/Pages/index.aspx.
[15] R.I. Gen. Laws §21-28.6 (2010). For more information, visit Rhode Island Department of Health: http://www.health.ri.gov/programs/medicalmarijuana/index.php

[16] Vt. Stat. Ann. tit. 18, §§ 4471-4474d (2010); and Vt. Senate Bill 17 (2011), http://www.leg.state.vt.us/docs/2012/Acts/ACT065.PD. For more information, visit Vermont Department of Public Safety: http://vcic.vermont.gov/marijuana_registry.

[17] Wash. Rev. Code § 69.51A (2010). For more information, visit Washington State Department of Health: http://www.doh.wa.gov/hsqa/medical-marijuana/.

[18] Initiative 59 (1998); "Legalization of Marijuana for Medical Treatment Amendment Act of 2010" (2010). For more information, visit D.C. Department of Health: http://hrla.doh.dc.gov/hrla/cwp/view,a,1385,q,578539.asp.

[19] For more information on most states' laws, see Mark Eddy, "CRS Report for Congress: Medical Marijuana: Review and Analysis of Federal and State Policies," Congressional Research Service, Order Code RL33211 Library of Congress, updated July 27, 2009, www.fas.org/sgp/crs/misc/RL33211.pdf

[20] According to the most credible estimates based on news reports and published information from state agencies, there are likely 1.1 – 1.5 million lawful medical marijuana patients currently using marijuana for their conditions in the 17 jurisdictions that allow it. *See* Russ Belville, "America's One Million Legalized Marijuana Users," NORML (May 31, 2011), http://blog.norml.org/2011/05/31/americas-one-million-legalized-marijuana-users/; and Ian Yarett, "Back Story: How High Are You?," *Newsweek* (February 15, 2010).

[21] John Ingold, "Medical-marijuana sales tax nets $2.2 million for Colorado this year," *The Denver Post* (November 23, 2010), http://www.denverpost.com/news/marijuana/ci_16688199#ixzz1bDrH6tZB; and Daniel Chacón, "Medical marijuana takes city to new sales tax high," Colorado Springs Gazette (October 07, 2010), http://www.gazette.com/articles/marijuana-105987-city-medical.html.

[22] See Change Strategy, "State of the Medical Marijuana Markets "(American Cannabis Research Institute, 2011).

[23] Sam Harper et al, "Do Medical Marijuana Laws Increase Marijuana Use? Replication Study and Extension," *Annals of Epidemiology* (2012),

[24] Sam Harper et al, "Do Medical Marijuana Laws Increase Marijuana Use? Replication Study and Extension," *Annals of Epidemiology* (2012),

[25] D. Mark Anderson, Benjamin Hansen, and Daniel I. Rees, *Medical Marijuana Laws and Teen Marijuana Use* (Bonn, Germany: Institute for the Study of Labor, 2012), http://ftp.iza.org/dp6592.pdf.

[26] Dennis M. Gorman & J. Charles Huber Jr., "Do medical cannabis laws encourage cannabis use? International Journal of Drug Policy 18 (2007) 160–167.

[27] "Legalizing Medical Marijuana Does Not Increase Use among Youth, Study Suggests," *ScienceDaily* (Nov. 2, 2011), http://www.sciencedaily.com/releases/2011/11/111102161047.htm.

[28] See for example, Paul Armentano, Cannabis and Driving: A Scientific and Rational Review NORML Report (2011 Update); http://norml.org/library/driving-and-marijuana; Marijuana DUI Workgroup and Recommendation to the Drug Policy Task Force and Colorado Commission on Criminal and Juvenile Justice - MMIG Report (2011), http://norml.org/pdf_files/MMIG_Workgroup_Recommendation_9-6-11.pdf.

[29] D. Mark Anderson, Daniel I. Rees, "Medical Marijuana Laws, Traffic Fatalities, and Alcohol Consumption," Institute for the Study of Labor (November 2011). http://www.iza.org/en/webcontent/publications/papers/viewAbstract?dp_id=6112 (emphasis added).

[30] See David Nutt, "Development of a rational scale to assess the harm of drugs of potential misuse," 396 *The Lancet* 1047–53 (2007). See also Wang T, Collet JP, Shapiro S, Ware MA. "Adverse effects of medical cannabinoids: a systematic review." CMAJ. 2008 Jun 17;178(13):1669-78. ("Most of the events were not serious. None of the reported adverse events was unexpected... we did not find a higher incidence rate of serious adverse events associated with medical cannabinoid use. ")

[31] David J Nutt, "Drug harms in the UK: a multicriteria decision analysis," 376 *Lancet* 1558–65 (2010).

[32] Janet Joy, et al., *Marijuana and Medicine: Assessing the Science Base*, Institute of Medicine (2001); Hall, et al., "*A Comparative Appraisal of the Health and Psychological Consequences of Alcohol, Cannabis, Nicotine and Opiate Use*," World Health Organization (1995).

[33] Joy, et al.

[34] Hall, et al. (emphasis added).

[35] See Van Gundy & Rebellon, "A Life-course Perspective on the 'Gateway Hypothesis'," 51 *Journal of Health and Social Behavior* 244–259; Morral, Andrew R., et al., "Reassessing the marijuana gateway effect," 97 *Addiction* 1493–1504 (2002).

[36] Morral, Andrew R., et al., "Reassessing the marijuana gateway effect," 97 *Addiction* 1493–1504 (2002).

[37] Joy, et al.

[38] Van Gundy & Rebellon.

[39] Joy, et al.

[40] Reuter, Peter, et al., *Cannabis Policy: Moving Beyond Stalemate: Report of the Global Cannabis Commission* (2010).

[41] Id.

[42] Reiman, Amanda, "Cannabis as a substitute for alcohol and other drugs," 6 *Harm Reduction Journal* 35 (2009).

[43] Nunberg, Helen, et al., "An Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice in California," *Journal of Drug Policy Analysis* (2011).

[44] D. Mark Anderson, Daniel I. Rees, Joseph J. Sabia, High on Life? Medical Marijuana Laws and Suicide, D. Mark Anderson, Daniel I. Rees, "Medical Marijuana Laws, Traffic Fatalities, and Alcohol Consumption," Institute for the Study of Labor (January 2012), http://www.iza.org/en/webcontent/publications/papers/viewAbstract?dp_id=6280.

[45] D I Abrams, et al. "Cannabinoid-Opioid interaction in chronic pain," *Clinical Pharmacology & Therapeutics (2011); 90 6, 844–851.*

[46] Mark Collen *"Prescribing cannabis for harm reduction" Harm Reduction Journal* (2012), 9:1, http://www.harmreductionjournal.com/content/pdf/1477-7517-9-1.pdf.

[47] See American College of Physicians, "Supporting Research into the Therapeutic Role of Marijuana" (2008), http://www.cmcr.ucsd.edu/geninfo/ACP_2008_v2.pdf ; American Public Health Association, "Resolution #9513, Access to Therapeutic Marijuana/Cannabis," 86 *American Journal of Public Health* 441–42 (1996) http://www.drugsense.org/tfy/apha.htm; American Nurses Association, "Providing Patients Safe Access to Therapeutic Marijuana/Cannabis" (2003), and "In Support of Patients' Safe Access to Therapeutic Marijuana" (2008) http://www.nursingworld.org/EthicsHumanRights; British Medical Association, "*Therapeutic Uses of Cannabis*" (1997); Canadian Medical Association (2006) www.cma.ca/index.cfm/ci_id/3396/la_id/1.htm; Leukemia & Lymphoma Society, "Medical Marijuana Use and Research," (2008) http://www.maps.org/mmj/lnls-res.pdf.

[48] American Medical Association, "Board Of Trustees and Council Reports – Recommendations" 14 http://www.ama-assn.org/assets/meeting/mm/i-09-statements-recommendations.pdf.

[49] For more detailed references and excerpts from these organizations' positions statements, visit: http://docs.mpp.org/pdfs/download-materials/Mmj-Endorsements_0908-NOLOGO.pdf; and http://norml.org/index.cfm?Group_ID=3390.