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Abuse of psychiatric medications: Not just stimulants and benzodiazepines

Anticholinergics, antidepressants, antipsychotics, and gabapentinoids may also be subject to misuse or abuse

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While some classes of medications used to treat psychiatric disorders, such as stimulants and benzodiazepines, are well-recognized as controlled substances and drugs of abuse, clinicians may be less familiar with the potential misuse/abuse of other psychiatric medications. This article reviews the evidence related to the misuse/abuse of anticholinergics, antidepressants, antipsychotics, and gabapentinoids.

The terms “misuse,” “abuse,” and “addiction” are used variably in the literature without standardized definitions. For this review, “misuse/abuse (M/A)” will be used to collectively describe self-administration that is recreational or otherwise inconsistent with legal or medical guidelines, unless a specific distinction is made. Whether or not the medications reviewed are truly “addictive” will be briefly discussed for each drug class, but the focus will be on clinically relevant aspects of M/A, including:

- excessive self-administration
- self-administration by non-oral routes
- co-administration with other drugs of abuse
- malingering of psychiatric symptoms to obtain prescriptions
- diversion for sale to third parties
- toxicity from overdose.

continued



Abuse of psychiatric medications

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Abusers sometimes take anticholinergics with alcohol in order to 'potentiate' the effects of each substance



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Anticholinergic medications

The first case describing the deliberate M/A of an anticholinergic medication for its euphoric effects was published in 1960. Further reports followed in Europe before the M/A potential of prescription anticholinergic medications among psychiatric patients with an overdose syndrome characterized by atropinism and toxic psychosis was more widely recognized in the United States in the 1970s. Most reported cases of M/A to date have occurred among patients with psychiatric illness because anticholinergic medications, including trihexyphenidyl, benztropine, biperiden, procyclidine, and orphenadrine, were commonly prescribed for the management of first-generation and high dopamine D2-affinity antipsychotic-induced extrapyramidal symptoms (EPS). For example, one study of 234 consecutively hospitalized patients with schizophrenia noted an anticholinergic M/A incidence of 6.5%.¹

However, anticholinergic M/A is not limited to individuals with psychotic disorders. A UK study of 154 admissions to an inpatient unit specializing in behavioral disturbances found a 12-month trihexyphenidyl M/A incidence of 17%; the most common diagnosis among abusers was antisocial personality disorder.² Anticholinergic M/A has also been reported among patients with a primary diagnosis of substance use disorders (SUDs)³ as well as more indiscriminately in prison settings,⁴ with some inmates exchanging trihexyphenidyl as currency and using it recreationally by crushing it into powder and smoking it with tobacco.⁵ Others have noted that abusers sometimes take anticholinergics with alcohol in order to "potentiate" the effects of each substance.^{6,7} Pullen et al⁸ described individuals with and without psychiatric illness who stole anticholinergic medications, purchased them from other patients, or bought them "on the street." Malingering EPS in order to obtain anticholinergic medications has also been well documented.⁹ Clearly, anticholinergic M/A can occur in psychiatric and non-psychiatric populations, both within and outside of clinical settings. Although anticholinergic M/A appears to be less frequent

in the United States now that second-generation antipsychotics (SGAs) are more frequently prescribed, M/A remains common in some settings outside of the United States.⁷

Among the various anticholinergic medications prescribed for EPS, trihexyphenidyl has been reported to have the greatest M/A potential, which has been attributed to its potency,¹⁰ its stimulating effects (whereas benztropine is more sedating),¹¹ and its former popularity among prescribers.⁸ Marken et al¹¹ published a review of 110 reports of M/A occurring in patients receiving anticholinergic medications as part of psychiatric treatment in which 69% of cases involved taking trihexyphenidyl 15 to 60 mg at a time (recommended dosing is 6 to 10 mg/d in divided doses). Most of these patients were prescribed anticholinergic medications for diagnostically appropriate reasons—only 7% were described as "true abusers" with no medical indication. Anticholinergic M/A was typically driven by a desire for euphoric and psychedelic/hallucinogenic effects, although in some cases, anticholinergic M/A was attributed to self-medication of EPS and depressive symptoms. These findings illustrate the blurred distinction between recreational use and perceived subjective benefit, and match those of a subsequent study of 50 psychiatric patients who reported anticholinergic M/A not only to "get high," but to "decrease depression," "increase energy," and decrease antipsychotic adverse effects.¹² Once again, trihexyphenidyl was the most frequently misused anticholinergic in this sample.

Table 1^{2,3,7,8,10-15} (page 13) outlines the subjective effects sought and experienced by anticholinergic abusers as well as potential toxic effects; there is the potential for overlap. Several authors have also described physiologic dependence with long-term trihexyphenidyl use, including tolerance and a withdrawal/abstinence syndrome.^{7,16} In addition, there have been several reports of coma¹³ and death in the setting of intended suicide by overdose of anticholinergic medications.^{14,15}

Although anticholinergic M/A in the United States now appears to be less

Table 1

Desired and toxic effects of anticholinergic misuse/abuse

Desired and reported subjective effects Toxic effects

Euphoria	Insomnia
Stimulation	“Atropinism” (dry mouth, blurred vision, tachycardia, anhidrosis, urinary retention)
Increased sociability	Aggression
Anxiolysis	Psychosis (hallucinations, paranoia, ideas of reference)
Increased energy	Temporal distortion
Disinhibition	Cognitive impairment
Enhanced sexual pleasure	Delirium
“Self-medication” of depressive, negative, and extrapyramidal symptoms	Hyperpyrexia
	Coma
	Death

Source: References 2,3,7,8,10-15

common, clinicians should remain aware of the M/A potential of anticholinergic medications prescribed for EPS. Management of M/A involves:

- detection
- reducing anticholinergic exposure by managing EPS with alternative strategies, such as switching or reducing the dose of the antipsychotic medication
- gradual tapering of anticholinergic medications to minimize withdrawal.¹¹

Antidepressants

Haddad¹⁷ published a review of 21 English-language case reports from 1966 to 1998 describing antidepressant use in which individuals met DSM-IV criteria for substance dependence to the medication. An additional 14 cases of antidepressant M/A were excluded based on insufficient details to support a diagnosis of dependence. The 21 reported cases involved:

- tranylcypromine (a monoamine oxidase inhibitor [MAOI])
- amitriptyline (a tricyclic antidepressant [TCA])
- fluoxetine (a selective serotonin reuptake inhibitor [SSRI])
- amineptine (a TCA previously available in France but removed from the market in 1999 in part due to its abuse potential)

- nomifensine (a norepinephrine/dopamine reuptake inhibitor previously available in the United Kingdom but removed in 1986 due to hemolytic anemia).

In 95% of cases, the antidepressants were prescribed for treatment of an affective disorder but were abused for stimulant effects or the perceived ability to lift mood, cause euphoria or a “high,” or to improve functioning. Two-thirds of cases involved patients with preexisting substance misuse. Placing the case reports in the context of the millions of patients prescribed antidepressants during this period, Haddad concluded the “incidence of [antidepressant] addiction [is] so low as to be clinically irrelevant.”¹⁷

Despite this conclusion, Haddad singled out amineptine and tranylcypromine as antidepressants with some evidence of true addictive potential.^{17,18} A more recent case series described 14 patients who met DSM-IV criteria for substance abuse of tertiary amine TCAs (which have strong anticholinergic activity) and concluded that “misuse of [TCAs] is more common than generally appreciated.”¹⁹ In keeping with that claim, a study of 54 outpatients taking unspecified antidepressants found that up to 15% met DSM-III-R criteria for substance dependence (for the antidepressant) in the past year, although that rate was much lower than the rate of benzodiazepine dependence

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Among the anticholinergics prescribed for EPS, trihexyphenidyl is reported to have the greatest misuse/abuse potential



Abuse of psychiatric medications

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Individuals who misuse bupropion often include those with existing SUDs but limited access to illicit stimulants

Table 2

Adverse events associated with bupropion misuse/abuse^a

Tachycardia (57.1%)
Seizures (33.5%)
Agitation (20.2%)
Psychosis (14.0%)
Tremor (13.1%)
Vomiting (12.0%)
Hypertension (10.2%)
Nausea (8.1%)
Confusion (7.4%)
Cardiac arrhythmia (2%)
Tissue necrosis (from injection, n = 2)
Death (incidental, n = 4)
^a Incidence based on reports to US Poison Control Centers
Source: References 28,30,32-34,36,39

(47%) in a comparative sample.²⁰ Finally, a comprehensive review by Evans and Sullivan²¹ found anecdotal reports published before 2014 that detailed misuse, abuse, and dependence with MAOIs, TCAs, fluoxetine, venlafaxine, bupropion, tianeptine, and amineptine. Taken together, existing evidence indicates that select individuals—typically those with other SUD comorbidity—sometimes misuse antidepressants in a way that suggests addiction.

Still, while it is well known that abrupt cessation of antidepressants can result in a discontinuation syndrome characterized by flu-like symptoms, nausea, and dizziness,²² physiologic withdrawal effects must be distinguished from historical definitions of substance “abuse” and the broader concept of psychological “addiction” or drug dependence^{18,23} now incorporated into the DSM-5 definition of SUDs.²⁴ Indeed, although withdrawal symptoms were reported by more than half of those who took antidepressants and responded to a recent online survey,²⁵ evidence to support the existence of significant antidepressant tolerance, craving, or compulsive use is lacking.^{17,18} Antidepressants as a class do not appear to be significantly rewarding or reinforcing and, on the contrary, discontinuation by patients is common in clinical

practice.²⁶ The popular claim that some individuals taking antidepressants “can’t quit”²⁷ must also be disentangled from loss of therapeutic effects upon cessation.

Bupropion. A more convincing argument for antidepressant addiction can be made for bupropion, a weak norepinephrine and dopamine reuptake inhibitor with an otherwise unclear mechanism of action.²⁸ In 2002, the first report of recreational bupropion M/A described a 13-year-old girl who took 2,400 mg orally (recommended maximum dose is 450 mg/d in divided doses) after being told it would give her “a better high than amphetamine.”²⁹ This was followed in the same year by the first report of recreational M/A of bupropion via nasal insufflation (snorting), resulting in a seizure,³⁰ and in 2013 by the first published case of M/A by IV self-administration.³¹

The M/A potential of bupropion, most commonly via intranasal administration, is now broadly recognized based on several case reports describing desired effects that include a euphoric high and a stimulating “buzz” similar to that of cocaine or methamphetamine but less intense.²⁹⁻³⁶ Among recreational users, bupropion tablets are referred to as “welbys,” “wellies,” “dubs,” or “barnies.”³⁷ Media coverage of a 2013 outbreak of bupropion M/A in Toronto detailed administration by snorting, smoking, and injection, and described bupropion as “poor man’s cocaine.”³⁸ Between 2003 and 2016, 2,232 cases of bupropion misuse/abuse/dependence adverse drug reactions were reported to the European Monitoring Agency.³⁷ A review of intentional bupropion M/A reported to US Poison Control Centers between 2000 to 2013 found 975 such cases, with the yearly number tripling between 2000 and 2012.³⁹ In this sample, nearly half (45%) of the users were age 13 to 19, and 76% of cases involved oral ingestion. In addition to bupropion M/A among younger people, individuals who misuse bupropion often include those with existing SUDs but limited access to illicit stimulants and those trying to evade detection by urine toxicology screening.³³ For example, widespread use and diversion has been well documented within correctional settings, and as a result, many

facilities have removed bupropion from their formularies.^{21,28,33,34,40}

Beyond desired effects, the most common adverse events associated with bupropion M/A are listed in *Table 2*^{28,30,32-34,36,39} (*page 14*), along with their incidence based on cases brought to the attention of US Poison Control Centers.³⁹ With relatively little evidence of a significant bupropion withdrawal syndrome,³⁷ the argument in favor of modeling bupropion as a truly addictive drug is limited to anecdotal reports of cravings and compulsive self-administration³⁵ and pro-dopaminergic activity (reuptake inhibition) that might provide a mechanism for potential rewarding and reinforcing effects.⁴⁰ While early preclinical studies of bupropion failed to provide evidence of amphetamine-like abuse potential,^{41,42} non-oral administration in amounts well beyond therapeutic dosing could account for euphoric effects and a greater risk of psychological dependence and addiction.^{21,28,40}

Bupropion also has an FDA indication as an aid to smoking cessation treatment, and the medication demonstrated early promise in the pharmacologic treatment of psychostimulant use disorders, with reported improvements in cravings and other SUD outcomes.⁴³⁻⁴⁵ However, subsequent randomized controlled trials (RCTs) failed to demonstrate a clear therapeutic role for bupropion in the treatment of cocaine^{46,47} and methamphetamine use disorders (although some secondary analyses suggest possible therapeutic effects among non-daily stimulant users who are able to maintain good adherence with bupropion).⁴⁸⁻⁵¹ Given these overall discouraging results, the additive seizure risk of bupropion use with concomitant psychostimulant use, and the potential for M/A and diversion of bupropion (particularly among those with existing SUDs), the use of bupropion for the off-label treatment of stimulant use disorders is not advised.

Antipsychotics

As dopamine antagonists, antipsychotics are typically considered to have low potential for rewarding or reinforcing effects.

Indeed, misuse of antipsychotics was a rarity in the first-generation era, with only a few published reports of haloperidol M/A within a small cluster of naïve young people who developed acute EPS,⁵² and a report of diversion in a prison with the “sadistic” intent of inflicting dystonic reactions on others.⁵³ A more recent report described 2 additional cases of M/A involving haloperidol and trifluoperazine.⁵⁴ Some authors have described occasional drug-seeking behavior for low-potency D2 blockers such as chlorpromazine, presumably based on their M/A as anticholinergic medications.⁵⁵

The potential for antipsychotic M/A has gained wider recognition since the advent of the SGAs. Three cases of prescription olanzapine M/A have been published to date. One involved a man who malingered manic symptoms to obtain olanzapine, taking ≥ 40 mg at a time (beyond his prescribed dose of 20 mg twice daily) to get a “buzz,” and combining it with alcohol and benzodiazepines for additive effects or to “come down” from cocaine.⁵⁶ This patient noted that olanzapine was “a popular drug at parties” and was bought, sold, or traded among users, and occasionally administered intravenously. Two other cases described women who self-administered olanzapine, 40 to 50 mg/d, for euphoric and anxiolytic effects.^{57,58} James et al⁵⁹ detailed a sample of 28 adults who reported “non-medical use” of olanzapine for anxiolytic effects, as a sleep aid, or to “escape from worries.”

Quetiapine. In contrast to some reports of olanzapine M/A in which the line between M/A and “self-medication” was blurred, quetiapine has become a more convincing example of clear recreational antipsychotic M/A. Since the first report of oral and intranasal quetiapine M/A in the Los Angeles County Jail published in 2004,⁵⁵ subsequent cases have detailed other novel methods of recreational self-administration⁶⁰⁻⁶⁸ (*Table 3*,^{55,60-68} *page 16*), and additional reports have been published in non-English language journals.^{69,70} Collectively, these case reports have detailed that quetiapine is:

- misused for primary subjective effects as well as to mitigate the unpleasant effects of other drugs^{60,67}

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The potential for antipsychotic misuse/abuse has gained wider recognition since the advent of the SGAs



Abuse of psychiatric medications

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Individuals often obtain quetiapine by malingering psychiatric symptoms

Table 3

Routes of administration of quetiapine misuse/abuse

Excessive oral dosing
Oral combination with alcohol, benzodiazepines, and gabapentin
Intranasal insufflation (snorting)
IV use
IV use in combination with cocaine (“Q-ball”)
Smoking with cannabis
Source: References 55,60-68

- referred to as “quell,” “Q,” “Susie-Q,” “squirrel,” and “baby heroin”^{55,71,72}
- often obtained by malingering psychiatric symptoms^{55,61,63,65}
- diverted/sold with “street value” both within and outside of psychiatric facilities and correctional settings.^{55,60-62,67,68,73}

These anecdotal accounts of quetiapine M/A have since been corroborated on a larger scale based on several retrospective studies. Although early reports of quetiapine M/A occurring in correctional settings have resulted in formulary removal,^{71,74} quetiapine M/A is by no means limited to forensic populations and is especially common among those with comorbid SUDs. A survey of 74 patients enrolled in a Canadian methadone program reported that nearly 60% had misused quetiapine at some point.⁷⁵ Among an Australian sample of 868 individuals with active IV drug abuse, 31% reported having misused quetiapine.⁷⁶ Finally, within a small sample of patients with SUDs admitted to a detoxification unit in New York City, 17% reported M/A of SGAs.⁷⁷ In this study, SGAs were often taken in conjunction with other drugs of abuse in order to “recover” from or “enhance” the effects of other drugs or to “experiment.” Quetiapine was by far the most frequently abused SGA, reported in 96% of the sample; the most frequently reported SGA/drug combinations were quetiapine/alcohol/opioids, quetiapine/cocaine, and quetiapine/opioids.

Looking more broadly at poison center data, reports to the US National Poison Data System (NPDS) from 2005 to 2011

included 3,116 cases of quetiapine abuse (37.5%, defined as intentional recreational use in order to obtain a “high”) or misuse (62.5%, defined as improper use or dosing for non-recreational purposes).⁷⁸ A more recent analysis of NPDS reports from 2003 to 2013 found 2,118 cases of quetiapine abuse, representing 61% of all cases of reported SGA abuse.⁷⁹ An analysis of the European Medicines Agency Adverse Drug Database yielded 18,112 reports of quetiapine misuse, abuse, dependence, and withdrawal for quetiapine (from 2005 to 2016) compared with 4,178 for olanzapine (from 2004 to 2016).⁸⁰ These reports identified 368 fatalities associated with quetiapine.

The rate of quetiapine M/A appears to be increasing sharply. Reports of quetiapine M/A to poison centers in Australia increased nearly 7-fold from 2006 to 2016.⁸¹ Based on reports to the Drug Abuse Warning System, US emergency department visits for M/A of quetiapine increased from 19,195 in 2005 to 32,024 in 2011 (an average of 27,114 visits/year), with 75% of cases involving quetiapine taken in combination with other prescription drugs, alcohol, or illicit drugs.⁸² Consistent with poison center data, M/A was reported for other antipsychotics, but none nearly as frequently as for quetiapine.

With increasingly frequent quetiapine M/A, clinicians should be vigilant in monitoring for medical morbidity related to quetiapine and cumulative toxicity with other drugs. The most frequent adverse events associated with quetiapine M/A reported to US Poison Control Centers are presented in **Table 4**^{78,79} (**page 21**).

Unlike bupropion, quetiapine’s dopamine antagonism makes it unlikely to be a truly addictive drug, although this mechanism of action could mediate an increase in concurrent psychostimulant use.⁸³ A few case reports have described a quetiapine discontinuation syndrome similar to that of antidepressants,^{60,65,84-88} but withdrawal symptoms suggestive of physiologic dependence may be mediated by non-dopaminergic effects through histamine and serotonin receptors.^{84,89} Evidence for quetiapine misuse being associated with craving and compulsive use is lacking, and true quetiapine addiction is probably rare.

Similar to bupropion, preliminary findings have suggested promise for quetiapine as a putative therapy for other SUDs.⁹⁰⁻⁹³ However, subsequent RCTs have failed to demonstrate a therapeutic effect for alcohol and cocaine use disorders.⁹⁴⁻⁹⁶ Given these negative results and the clear M/A potential of quetiapine, off-label use of quetiapine for the treatment of SUDs and psychiatric symptoms among those with SUDs must be considered judiciously, with an eye towards possible diversion and avoiding the substitution of one drug of abuse for another.

Gabapentinoids

In 1997, the first published case report of gabapentin M/A described a woman who self-administered her husband's gabapentin to reduce cravings for and withdrawal from cocaine.⁹⁷ The authors highlighted the possible therapeutic benefit of gabapentin in this regard rather than raising concerns about diversion and M/A. By 2004, however, reports of recreational gabapentin M/A emerged among inmates incarcerated within Florida correctional facilities who self-administered intranasal gabapentin to achieve a "high" that was "reminiscent of prior effects from intranasal ingestion of cocaine powder."⁹⁸ In 2007, a single case of gabapentin misuse up to 7,200 mg/d (recommended dosing is $\leq 3,600$ mg/d) was reported, with documentation of both tolerance and withdrawal symptoms.⁹⁹ As of 2017, a total of 36 cases of gabapentin M/A and 19 cases of pregabalin M/A have been published.¹⁰⁰

In the past decade, anecdotal reports have given way to larger-scale epidemiologic data painting a clear picture of the now-widespread M/A of gabapentin and other gabapentinoids. For example, a study of online descriptions of gabapentin and pregabalin M/A from 2008 to 2010 documented:

- oral and IM use (gabapentin)
- IV and rectal ("plugging") use (pregabalin)
- "parachuting" (emptying the contents of capsules for a larger dose) (pregabalin)
- euphoric, entactogenic, stimulant, calming/anxiolytic, and dissociative subjective effects (gabapentin/pregabalin)

Table 4

Adverse events associated with quetiapine misuse/abuse^a

Sedation (51% to 54%)
Tachycardia (23% to 25%)
Slurred speech (7% to 8%)
Dizziness (5% to 6%)
Hypotension (5% to 6%)
Agitation/irritability (5%)
Confusion (4%)
Ataxia (3% to 4%)
Nausea (2%)
Seizures (1%)
Respiratory depression (1%)
Coma (1%)

^aIncidence based on reports to the US National Poison Data System

Source: References 78,79

- rapid development of tolerance to euphoric effects leading to self-administration of increasing doses (gabapentin/pregabalin)

- frequent co-administration with other drugs of abuse, including alcohol, benzodiazepines, cannabis, stimulants, opiates, hallucinogens, gamma-hydroxybutyrate, mephedrone, and *Salvia divinorum* (gabapentin/pregabalin)¹⁰¹

Several systematic reviews of both anecdotal reports and epidemiologic studies published in the past few years provide additional evidence of the above, such as:

- excessive dosing with self-administration
- intranasal and inhaled routes of administration
- diversion and "street value"
- greater M/A potential of pregabalin than gabapentin
- the presence of gabapentinoids in post-mortem toxicology analyses, suggesting a role in overdose fatalities when combined with other drugs.^{100,102,103}

The European Medicine Agency's EudraVigilance database included 4,301 reports of gabapentin misuse, abuse, or dependence, and 7,639 such reports for pregabalin, from 2006 to 2015 (rising sharply after 2012), with 86 gabapentin-related and 27 pregabalin-related fatalities.¹⁰⁴ Data from the

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Several systematic reviews of gabapentinoids have provided evidence of excessive dosing with self-administration



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When prescribing gabapentinoids to manage psychiatric symptoms, carefully consider the risk of misuse/abuse in patients with SUDs

Drug Diversion Program of the Researched Abuse, Diversion, and Addiction-Related Surveillance System from 2002 to 2015 have likewise revealed that gabapentin diversion increased significantly in 2013.¹⁰⁵

While the prevalence of gabapentinoid M/A is not known, rates appear to be significantly lower than for traditional drugs of abuse such as cannabis, cocaine, 3,4-methylenedioxymethamphetamine (MDMA), and opioids.^{106,107} However, gabapentin and pregabalin M/A appears to be increasingly common among individuals with SUDs and in particular among those with opioid use disorders (OUDs). For example, a 2015 report indicated that 15% of an adult cohort in Appalachian Kentucky with nonmedical use of diverted prescription opioids reported gabapentin M/A, an increase of nearly 3,000% since 2008.¹⁰⁸ Based on data from a US insurance enrollment and claims database, researchers found that the rate of gabapentin overuse among those also overusing opioids was 12% compared with only 2% for those using gabapentin alone.¹⁰⁹ It has also been reported that gabapentin is sometimes used as a “cutting agent” for heroin.¹¹⁰

Those who use gabapentinoids together with opioids report that gabapentin and pregabalin potentiate the euphoric effects of methadone¹¹¹ and endorse specific beliefs that pregabalin increases both the desired effects of heroin as well as negative effects such as “blackouts,” loss of control, and risk of overdose.¹¹² Indeed, sustained M/A of gabapentin and opioids together has been found to increase emergency department utilization, drug-related hospitalization, and respiratory depression.¹¹³ Based on a case-control study of opioid users in Canada, co-prescription of gabapentin and opioids was associated with a 50% increase in death from opioid-related causes compared with prescription of opioids alone.¹¹⁴

Case reports documenting tolerance, withdrawal, craving, and loss of control suggest a true addictive potential for gabapentinoids, but Bonnet and Sherbaum¹⁰⁰ concluded that while there is robust evidence of abusers “liking” gabapentin and pregabalin (eg, reward), evidence of “wanting” them (eg, psychological dependence)

in the absence of other SUDs has been limited to only a few anecdotal reports with pregabalin. Accordingly, the risk of true addiction to gabapentinoids by those without preexisting SUDs appears to be low. Nonetheless, the M/A potential of both gabapentin and pregabalin is clear and in the context of a nationwide opioid epidemic, the increased morbidity/mortality risk related to combined use of gabapentinoids and opioids is both striking and concerning. Consequently, the state of Kentucky recently recognized the M/A potential of gabapentin by designating it a Schedule V controlled substance (pregabalin is already a Schedule V drug according to the US Drug Enforcement Agency),^{103,113} and several other states now mandate the reporting of gabapentin prescriptions to prescription drug monitoring programs.¹¹⁵

Following a similar pattern to antidepressants and antipsychotics, a potential role for gabapentin in the treatment of cocaine use disorders was supported in preliminary studies,¹¹⁶⁻¹¹⁸ but not in subsequent RCTs.¹¹⁹⁻¹²¹ However, there is evidence from RCTs to support the use of gabapentin and pregabalin in the treatment of alcohol use disorders.¹²²⁻¹²⁴ Gabapentin was also found to significantly reduce cannabis use and withdrawal symptoms in patients compared with placebo in an RCT of individuals with cannabis use disorders.¹²⁵ The perceived safety of gabapentinoids by clinicians, their subjective desirability by patients with SUDs, and efficacy data supporting a therapeutic role in SUDs must be balanced with recognition that approximately 80% of gabapentin prescriptions are written for off-label indications for which there is little supporting evidence,¹⁰⁹ such as low back pain.¹²⁶ Clinicians considering prescribing gabapentinoids to manage psychiatric symptoms, such as anxiety and insomnia, should carefully consider the risk of M/A and other potential morbidities, especially in the setting of SUDs and OUD in particular.

Problematic, even if not addictive

It is sometimes claimed that “addiction” to psychiatric medications is not limited

to stimulants and benzodiazepines.^{27,127} Although anticholinergics, antidepressants, antipsychotics, and gabapentinoids can be drugs of abuse, with some users reporting physiologic withdrawal upon discontinuation, there is only limited evidence that the M/A of these psychiatric medications is associated with the characteristic features of a more complete definition of “addiction,” which may include:

- inability to consistently abstain
- impairment in behavioral control
- diminished recognition of significant problems associated with use
- a dysfunctional emotional response to chronic use.¹²⁸

Nonetheless, the literature documenting anticholinergic, antidepressant, antipsychotic, and gabapentinoid M/A includes several common features, including:

- initial reports among those with limited access to illicit drugs (eg, young people and incarcerated individuals) and subsequent spread to a wider population with more unconventional routes of administration
- use for recreational purposes and other subjective pseudo-therapeutic effects, often in combination with alcohol and illicit drugs
- greater M/A potential of certain medications within each of these drug classes (eg, trihexyphenidyl, bupropion, quetiapine)
- malingering psychiatric symptoms in order to obtain medications from prescribers and diversion for black market sale
- observations that medications might constitute therapy for SUDs that were not supported in subsequent RCTs (with the exception of gabapentin for alcohol and cannabis use disorders)
- increasing evidence of toxicity related to M/A, which suggests that prescription

Related Resources

- Substance Abuse and Mental Health Services Administration. Prescription drug misuse and abuse. <https://www.samhsa.gov/topics/prescription-drug-misuse-abuse>.
- Substance Abuse and Mental Health Services Administration. Types of commonly misused or abused drugs. <https://www.samhsa.gov/prescription-drug-misuse-abuse/types>.
- National Institute on Drug Abuse. Misuse of prescription drugs. <https://www.drugabuse.gov/publications/research-reports/misuse-prescription-drugs/summary>.
- National Institute on Drug Abuse. New clinician screening tool available for substance use. <https://www.drugabuse.gov/news-events/news-releases/2018/06/new-clinician-screening-tool-available-substance-use>.

Drug Brand Names

Amitriptyline • Elavil, Endep	Pregabalin • Lyrica, Lyrica CR
Benzotropine • Cogentin	Prochlorperazine • Compazine
Biperiden • Akineton	Quetiapine • Seroquel
Bupropion • Wellbutrin, Zyban	Tianeptine • Coaxil, Stablon
Chlorpromazine • Thorazine	Tranylcypromine • Parnate
Fluoxetine • Prozac	Trifluoperazine • Stelazine
Haloperidol • Haldol	Trihexyphenidyl • Artane, Tremin
Olanzapine • Zyprexa	Venlafaxine • Effexor
Orphenadrine • Disipal, Norflex	

by clinicians has limited benefit and high risk for patients with SUDs.

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continued

Clinical Point

There is only limited evidence that misuse/abuse of these medications is associated with characteristic features of ‘addiction’

Bottom Line

Some psychiatric medications are taken as drugs of abuse. Clinicians should be particularly aware of the misuse/abuse potential of anticholinergics, antidepressants, antipsychotics, and gabapentinoids, and use them cautiously, if at all, when treating patients with existing substance use disorders.



Abuse of psychiatric medications

Clinical Point

Anticholinergics, antidepressants, antipsychotics, and gabapentinoids may be used for pseudo-therapeutic effects

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Abuse of psychiatric medications

Clinical Point

The potential for misuse/abuse may be greater for trihexyphenidyl, bupropion, and quetiapine

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