Management of common adverse effects of antipsychotic medications

T. Scott Stroup[1], Neil Gray[2]

[1]New York State Psychiatric Institute, Columbia University College of Physicians and Surgeons, New York, NY, USA; [2]Department of Psychiatry, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA

The benefits of antipsychotic medications are sometimes obscured by their adverse effects. These effects range from relatively minor tolerability issues (e.g., mild sedation or dry mouth) to very unpleasant (e.g., constipation, akathisia, sexual dysfunction) to painful (e.g., acute dystonias) to disfiguring (e.g., weight gain, tardive dyskinesia) to life-threatening (e.g., myocarditis, agranulocytosis). Importantly, adverse effect profiles are specific to each antipsychotic medication and do not neatly fit into first- and second-generation classifications. This paper reviews management strategies for the most frequent side effects and identifies common principles intended to optimize net antipsychotic benefits. Only use antipsychotics if the indication is clear; only continue antipsychotics if a benefit is discernible. If an antipsychotic is providing substantial benefit, and the adverse effect is not life-threatening, then the first management choice is to lower the dose or adjust the dosing schedule. The next option is to change the antipsychotic; this is often reasonable unless the risk of relapse is high. In some instances, behavioral interventions can be tried. Finally, concomitant medications, though generally not desirable, are necessary in many instances and can provide considerable relief. Among concomitant medication strategies, anticholinergic medications for dystonias and parkinsonism are often effective; beta-blockers and anticholinergic medications are useful for akathisia; and metformin may lead to slight to moderate weight loss. Anticholinergic drops applied sublingually reduce sialorrhea. Usual medications are effective for constipation or dyslipidemias. The clinical utility of recently approved treatments for tardive dyskinesia, valbenazine and deutetrabenazine, is unclear.

Key words: Antipsychotics, adverse effects, schizophrenia, akathisia, tardive dyskinesia, parkinsonism, dystonias, impulse control disorders, sialorrhea, sedation, sexual function, orthostatic hypotension, neuroleptic malignant syndrome, metabolic effects, agranulocytosis

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Antipsychotics are the first-line evidence-based treatment for schizophrenia and other primary psychotic disorders. Some antipsychotics are also approved for treatment of bipolar disorder, treatment-resistant depression, autism, or Tourette's disorder. In addition, these medications are prescribed off-label for individuals with other conditions, such as borderline personality disorder, obsessive-compulsive disorder, anorexia nervosa, insomnia, delirium, and various dementia syndromes including Alzheimer's disease. The utility of these drugs is hampered by their adverse effects, which must be weighed against their variable benefits for these conditions.

In persons with schizophrenia, antipsychotic medications often provide dramatic symptomatic relief for hallucinations and delusions, and improvement for disorganized thoughts and behavior. However, because they are associated with a multitude of adverse effects, some of which are medically serious and many of which affect patient attitudes toward treatment, discussions about these medications are often dominated by their side effects rather than their benefits. This is highlighted by the fact that experts and guidelines commonly recommend choosing antipsychotic medications based on side effect profiles, which vary considerably, rather than efficacy, which is considered to be similar[1,2]. For non-psychotic disorders and for off-label uses, for which the evidence of antipsychotic benefits is often unclear, side effects are vitally important, because the ratio of benefits to risks is lower and significantly influences the decision to use these medications.

Risk-benefit assessments about whether to prescribe an antipsychotic medication for an individual should be made according to specific drugs (as opposed to "generation" or "class" of drug) and the specific situation (i.e., actual benefits and harms expected or experienced by an individual). Because the benefits of antipsychotics are sometimes obscured by the adverse effects and medical risks, understanding how such problems can be avoided and successfully managed is essential to optimize the use of these important but sometimes controversial medications.

RISKS AND SIDE EFFECTS OVERVIEW

The adverse effects of antipsychotic medications range from relatively minor tolerability issues (e.g., mild sedation or dry mouth) to very unpleasant (e.g., constipation, akathisia, sexual dysfunction) to painful (e.g., acute dystonias) to disfiguring (e.g., weight gain, tardive dyskinesia) to life threatening (e.g., myocarditis, agranulocytosis). Some adverse effects have little short-term clinical implications (e.g., increased prolactin or serum lipid levels), but may involve long-term risk of medical complications.

Each antipsychotic medication has a unique side effect profile, which affects individuals differently. Because the incidence of the side effects varies considerably across the large number of antipsychotic medications, we provide Table 1, which estimates the relative liability of commonly used drugs to cause specific adverse effects. The table demonstrates that the drugs' profiles do not adhere closely to first- and second-generation classifications of antipsychotics. With the important exception of tardive dyskinesia, which is more common among patients treated with older (first-generation) medications such as chlorpromazine and haloperidol, no adverse effect is class-specific. Weight gain is not unique to newer drugs,

Table 1 Side effect profiles of selected antipsychotic drugs

Adverse effects	AMI	ARI	CPZ	CLO	HAL	LUR	OLA	PAL	PER	QUE	RIS	SER	ZIP
Anticholinergic effects	0	0	++	+++	0	0	++	0	0/+	+/++	0	0	0
Acute parkinsonism	+	+	+	0	+++	+/++	0/+	++	++	0	++	0/+	+
Akathisia	+	++	+	+	+++	+/++	+	+	++	+	+	+	+/++
Tardive dyskinesia	0/+	0/+	++	0	++	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+
Diabetes	0/+	0/+	+++	+++	0/+	0/+	+++	+	+	++	+	+	0/+
Weight gain	0/+	0/+	+++	+++	+	0/+	+++	++	++	++	++	++	0/+
Increased lipids	+	0/+	+++	++	0/+	0/+	+++	+	+	++	+	+	0/+
Sialorrhea	0	0	0	++	0	0	0	0	0	0	0	0	0
Neutropenia	0/+	0/+	0/+	+++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+
Orthostatic hypotension	0/+	0/+	++	++	0	0/+	+	+	+	++	+	++	0
Hyperprolactinemia	+++	0	+	+	++	+	+	+++	++	0	+++	+	+
Increased QTc interval	++	0/+	0/+	++	0+	0/+	0/+	+	+	+	+	++/+++	++
Sedation	0/+	0/+	++	+++	+	+/++	+/++	0/+	+	++ b	+	0/+	+
Seizures	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+

AMI – amisulpride, ARI – aripiprazole, CPZ – chlorpromazine, CLO – clozapine, HAL – haloperidol, LUR – lurasidone, OLA – olanzapine, PAL – paliperidone, PER – perphenazine, QUE – quetiapine, RIS – risperidone, SER – sertindole, ZIP – ziprasidone, 0: none or equivocal, 0/+: minimal/rare, +: mild/sometimes occurs, ++: moderate/occurs frequently, +++: severe/occurs very often

nor is it present in all of the newer medications. Similarly, akathisia and parkinsonism are common with older drugs and some newer drugs. Several adverse effects – seizures, neutropenia, sialorrhea – are virtually unique to clozapine.

Some population groups respond distinctively to antipsychotics. For example, children, adolescents and the elderly are more likely to experience certain adverse effects or experience them more severely. Youth are more susceptible to weight gain and sedation, while the elderly are more vulnerable to consequences of orthostatic hypotension (falls) and anticholinergic effects (cognitive impairment). In addition, individuals vary considerably in their risk of side effects and how these effects are experienced.

PRINCIPLES FOR ANTIPSYCHOTIC PRESCRIBING

Before discussing the management of specific adverse effects, we propose some general principles for optimal prescribing of antipsychotic medications. First, only prescribe antipsychotics when a clear benefit can be expected and there is no safer or feasible alternative. Second, choose an antipsychotic based on the clinical situation and preferences of the patient (e.g., avoid medications that cause orthostatic hypotension in the elderly; avoid medications associated with substantial weight gain in patients who prioritize weight control; avoid QTc-prolonging drugs in patients with a history of heart disease, arrhythmia or syncope). Third, use the lowest effective dose of antipsychotic medication, which must be determined empirically for each individual. Fourth, discontinue the antipsychotic if there is no benefit. Often there is at least some benefit, signaling the need for an individualized risk-benefit assessment if there are side effects. Finally, monitor for known side effects regularly (see Table 2). The rest of this paper addresses what to do when adverse effects occur.

GENERAL STRATEGIES FOR MANAGING THE ADVERSE EFFECTS OF ANTIPSYCHOTICS

Antipsychotics that are not beneficial or are not required should be discontinued. The main strategies for managing adverse effects are as follows:

Lower the dose. This is relevant when the antipsychotic has provided benefit, and the adverse effect is dose-related and not medically urgent. Using the lowest dose that is effective at achieving treatment goals is widely recommended and reduces dose-related effects such as parkinsonism, sedation, hyperprolactinemia, orthostatic hypotension, and anticholinergic effects. In practice, finding the optimal, lowest effective dose is an individualized, empirical process that must balance the desires for maximal efficacy and minimal adverse effects[3].

Switch to an antipsychotic with a different adverse effect profile. Switching to a medication not likely to cause the problematic effect is a common strategy proven effective for at least some adverse effects, for example to address dyslipidemias or reduce weight[4,5]. Variability among antipsychotic medications in the risk for akathisia, parkinsonism and hyperprolactinemia makes switching an attractive approach to these problems, and evidence from observational and randomized trials sup-

Table 2 Suggested monitoring schedule for individuals taking antipsychotic medications

	Baseline	Each visit	During titration	At 3 months	Quarterly	Every 6 months	Annually
Weight	X		X		X		
Tardive dyskinesia (Abnormal Involuntary Movement Scale)	X		X			X	
Parkinsonism, akathisia	X		X				X
Glucose metabolism (fasting blood sugar, HbA1C)	X			X			X
Lipid metabolism (fasting lipids)	X			X			X
Blood pressure and pulse	X		X	X			X
Sexual/reproductive function	X		X				X
Sedation	X	X					
ECG (based on history and symptoms)	X						
Prolactin	If symptoms of hyperprolactinemia develop						

If taking clozapine, monitor for neutropenia, myocarditis and sialorrhea; if taking aripiprazole, cariprazine or brexpiprazole, monitor for impulse control disorders/behavioral addictions

ports this[4,5]. Switching is ideally done gradually rather than abruptly, to avoid symptom exacerbation and other rebound phenomena. A cross-titration completed within two to four weeks was adequate in one randomized controlled trial[5]. A risk when switching from an antipsychotic that has been effective is that the new medication may not be as efficacious; therefore patients undergoing switches should be monitored carefully for symptom exacerbations. Unless an individual has only responded to clozapine, switching antipsychotics is a preferred approach to deal with adverse effects that cannot be addressed with dosage adjustments.

Use a non-pharmacologic intervention. Non-pharmacologic interventions to reduce adverse effects are appealing but generally unavailable. Diet and exercise programs are modestly effective in addressing weight gain and related lipid abnormalities[6].

Treat with a concomitant medication. Using medications to manage antipsychotic side effects is a common but often suboptimal approach, because the beneficial effects of concomitant medications are often modest, they also may have adverse effects, and drug interactions may occur. For example, anticholinergic medications used to treat parkinsonism are associated with cognitive impairment and constipation. Further, few concomitant medication approaches are supported by evidence from randomized controlled trials.

In the following section, we describe common antipsychotic adverse effects and approaches to their prevention and management (see also Table 3). We focus on the most common and consequential adverse effects rather than the many possible but relatively rare effects. Our emphasis is on evidence-based management strategies, but in many instances the evidence is based on common sense and case reports rather than randomized controlled trials.

SPECIFIC ADVERSE EFFECTS

Neurologic side effects

Neurologic side effects known as extrapyramidal symptoms are prominent with antipsychotic medications, and the risk varies considerably among the individual antipsychotics, with high-potency drugs such as haloperidol carrying the greatest risk (Table 1). Principal manifestations include dystonias, akathisia and parkinsonism; tardive syndromes are discussed separately below. Dystonias are involuntary contractions of antagonistic muscle groups, leading to twisting, sustained and repetitive motions or abnormal postures, most commonly in the head, face and neck. These can be painful and highly distressing. Akathisia refers to a feeling of restlessness and tension that usually (but not always) compels the sufferer to near-constant motion, inducing dysphoria and even suicidality[7]. Parkinsonism includes a number of drug-induced symptoms resembling Parkinson's disease, such as bradykinesia, rigidity and tremor.

Dystonias typically occur within hours to days of antipsychotic administration or dose increase, almost always within the first five days[8]. Prevalence varies widely based on specific medication and risk factors[9]. A history of extrapyramidal side effects is the most significant risk factor, with a relative risk of about six[10]. Young age and male sex are also clear risk factors[10-12]. The two most concerning presentations are laryngospasm, which is rare but life-threatening[13], and oculogyric crisis, a highly painful and distressing tonic deviation of the eyes that can become recurrent or chronic[14].

Because dystonias are painful and highly distressing, prevention is the best management strategy. The mainstay of prophylaxis for dystonias is anticholinergic medication. Benztropine prophylaxis is effective for high-potency antipsycho-

Table 3 Common antipsychotic adverse effects and management strategies

Adverse effects	First choice	Second choice	Third choice	Others/Comments
Dystonias	Anticholinergic medication	Antihistaminic medication	Benzodiazepine	
Parkinsonism (tremor, rigidity, bradykinesia)	Lower dose	Change to antipsychotic with lower risk	Concomitant use of anticholinergic agent	
Akathisia	Lower dose	Change antipsychotic	Concomitant use of beta-blocker	Anticholinergics and benzodiazepines
Tardive dyskinesia	Lower dose	Valbenazine or deutetrabenazine	Gingko biloba or clonazepam	
Sialorrhea	Conservative approaches such as sugarless gum during day, towel over pillow at night	Anticholinergic drops (ipratropium or atropine) topically/sublingually		
Sedation	Dose at night before sleep	Lower dose	Change to less sedating antipsychotic	Stimulants have unclear benefit
Prolactin elevation, sexual side effects	Dose reduction	Change to a prolactin-sparing antipsychotic	Add aripiprazole	Phosphodiesterase inhibitors for sexual dysfunction
Orthostatic hypotension	Adjust dose or dosing schedule	Behavioral changes including adequate hydration	Change antipsychotic	Concomitant medication strategies are limited
QT prolongation	Change antipsychotic			Avoid other QT-prolonging agents
Neuroleptic malignant syndrome	Discontinue antipsychotic	Supportive measures including IV hydration and cooling	Dantrolene and bromocriptine	
Neutropenia/agranulocytosis	Discontinue clozapine or other causative agent	Colony-stimulating factors (e.g., filgastram)		
Impulse control disorders/ behavioral addictions	Change antipsychotic			
Myocarditis	Discontinue clozapine or other causative agent			
Weight gain, dyslipidemia	Behavioral modification (diet, exercise)	Change antipsychotic	Metformin	
Anticholinergic effects (dry mouth, blurry vision, tachycardia, constipation)	Lower dose	Change antipsychotic	Treat symptoms, e.g., constipation with osmotic agents, stimulant laxatives; tachycardia with beta-blocker	Limit other anticholinergic agents

tics[15-18], but may be ineffective for low-potency medications[19]. There is not yet consensus on when prophylaxis is indicated, but clinical judgment of relative risk of dystonias versus risk of anticholinergic side effects and polypharmacy suggests many cases in which prophylaxis is clearly indicated (e.g., a young male starting a high-potency antipsychotic). Prophylaxis should always be used if a patient is getting a first dose of a high-potency antipsychotic, such as haloperidol, by injection. Once a patient is on a stable dose of antipsychotic and anticholinergic, gradual withdrawal of the anticholinergic may be possible[20], though a quarter of patients may require reinstatement[21]. For patients who have dystonias on a high-potency antipsychotic, switching to a lower potency antipsychotic may reduce the risk of dystonias as well as parkinsonism[22].

In acute dystonic reactions requiring urgent treatment, intramuscular anticholinergics (e.g., biperiden 5 mg) or antihistaminics (e.g., diphenhydramine 50 mg) are indicated[9]. Multiple doses may be required for initial response, and are usually needed for 1-2 days to maintain response until the causative antipsychotic is cleared. Benzodiazepines are also thought to be effective in treating dystonias[23,24].

Parkinsonism typically presents insidiously over days to months[8]. In contrast to dystonias, risk of parkinsonism is greater in women and older patients[25]. Additional risk factors include pre-existing rigidity[26] and AIDS[27,28]. Treatment of psychosis in patients with Parkinson's disease is complex, and reviewed elsewhere[29-31].

In the treatment of antipsychotic-induced parkinsonism, reducing dose should be a first consideration[32]; switching from an antipsychotic with high risk to one of low risk can also be an effective strategy[33]. Concomitant medications are a third common approach that is useful if switching antipsychotics is not

desirable. Anticholinergic medications are useful in the treatment of parkinsonism, but this has not been thoroughly studied[34,35]; the risks of anticholinergic agents are greater in the elderly (who are more likely to be affected by parkinsonism). Benztropine, which is in common use, and ethopropazine, which may not be widely available, are anticholinergic medications known to be effective for parkinsonism[36,37]. Amantadine at 100-400 mg daily also has good support in the literature[36,38-40], and may be particularly helpful in elderly patients who need to avoid anticholinergic effects[32].

Akathisia typically develops gradually over days to weeks of treatment, though it can present more acutely[41]. There is not strong evidence for risk factors, other than current antipsychotic dose and rate of dose increment[42,43]. Akathisia occurs with many antipsychotics, with high-potency agents and aripiprazole being particularly prone to this side effect, while clozapine, olanzapine and quetiapine are low-risk[44,45].

Centrally-acting beta-adrenergic antagonists, primarily propranolol, have long been used as first-line therapy for akathisia with moderate efficacy[45,46], supported by multiple small placebo-controlled trials[47-50]. Orthostatic hypotension and bradycardia are significant drawbacks to beta-blockers. Anticholinergics such as benztropine have also been used clinically for akathisia, but their usefulness has not been demonstrated in a systematic way[51]. Anticholinergics may work best for akathisia when it co-occurs with parkinsonism[52].

Serotonergic treatments have gathered increasing attention for treatment of akathisia. The antidepressant mirtazapine at 15 mg/day has shown propranolol equivalency in several trials and seems to be well tolerated in the short term[43,50,51], though its potential to cause weight gain is a particular consideration among those receiving antipsychotics. The specific 5-HT2A/C antagonists mianserin and ritanserin have also shown efficacy in small open-label studies[52-58]. Zolmitriptan (a 5-HT1B/1D agonist) and cyproheptadine (which has 5-HT2 antagonism in addition to anticholinergic and antihistaminergic properties) were both found to be as effective as propranolol in small randomized trials[59,60].

Benzodiazepines are also commonly used to treat akathisia. In severe, acute cases, intravenous diazepam has produced rapid resolution of symptoms[61]. Clonazepam and lorazepam have shown utility in several small trials[62-64], with at least some evidence of a dose-response relationship. Further studies, particularly long-term trials given the tolerance that develops to these medications, are required[65]. A possible association of benzodiazepines with increased mortality rates in schizophrenia dampens enthusiasm for this approach[66].

Several other approaches to akathisia have been explored, but have very limited empirical support. High dose vitamin B6 (600 mg/day) was shown to provide subjective improvement in a small blinded trial[67], but this dose risks peripheral neuropathy in long-term treatment[68]. Clonidine has shown similar efficacy to beta-blockers, but with poorer tolerability[52]. Diphenhydramine has produced mixed results in small trials of akathisia induced by metoclopramide and prochlorperazine[69-71].

Tardive syndromes

Tardive dyskinesia is one of the most dreaded complications of antipsychotic treatment, though it may also occur with other medication classes[72]. It typically develops after months or years of exposure, and is characterized by involuntary athetoid or choreiform movements of the lower face, extremities and/or trunk muscles. Most commonly, these present as grimacing, lip-smacking/puckering, tongue movements, and excessive blinking. Most distressingly, symptoms persist long after the offending medication is discontinued, and may be permanent in some cases (dyskinesia lasting less than a month after withdrawal is considered a separate clinical entity, withdrawal dyskinesia). Other tardive manifestations may include akathisia, stereotypies, dystonias, parkinsonism, tremor, myoclonus, and tourettism[73].

Estimates of prevalence have varied, but a large systematic review of nearly 40,000 patients published in 1992 suggested that about 24% of those treated with antipsychotics had tardive dyskinesia[74]; the prevalence is thought to have declined since then due to the use of newer medications and more moderate dosing. Risk factors for the syndrome include early presence of extrapyramidal symptoms[75], and possibly African ethnicity and older age[72,74,76]. Female sex may also increase the risk[72,74], though there is conflicting evidence[76-78]. The early presence of extrapyramidal symptoms is a particularly useful risk factor, potentially allowing clinicians to reduce dose or switch antipsychotic before tardive dyskinesia is induced. There is an association of anticholinergic medication use with tardive dyskinesia which remains unexplained[77]; perhaps the presence of extrapyramidal symptoms explains this correlation.

Many studies have attempted to characterize genetic risk factors for tardive dyskinesia. In general, there have as yet been no findings conclusive enough, and with sufficient effect size, to warrant screening. Variations in catechol-O-methyltransferase[79,80], brain-derived neurotrophic factor (BDNF)[81], dopamine receptor 2[82], and manganese superoxide dismutase[79] genes have modest evidence for increasing risk. There is also mounting evidence that polymorphisms in genes involved in GABA and serotonergic signaling may confer risk[83-85]. It seems likely that, with continued effort, a clinically useful genetic screening test for tardive dyskinesia risk might be developed in the near future[83].

Newer (second-generation) antipsychotics are less likely to cause tardive dyskinesia[85], with annual incidence estimated at 3.9% (vs. 5.5% for first-generation drugs) in a review of twelve trials[86]. This differential of risk may be more pronounced in the elderly[87,88]. In a patient who has developed tardive dyskinesia on a first-generation antipsychotic, common clinical prac-

tice is to switch to a second-generation drug, but the empirical evidence to support this is weak; this has only been studied in small trials of risperidone and olanzapine[89-91]. Dosage reduction is also commonly recommended to prevent worsening of tardive dyskinesia, but again there is little evidence for this practice[92].

Many pharmaceutical strategies for tardive dyskinesia have been explored. Inhibitors of vesicular monoamine transporter 2 (VMAT2) are most notable: valbenazine was recently approved by the US Food and Drug Administration (FDA)[93]. The closely related medication tetrabenazine, approved for Huntington's disease but used off-label for a variety of hyperkinetic movement disorders, has also shown utility in treating tardive dyskinesia[94,95]. It is unclear to what extent these drugs differ in safety or efficacy[96]. Deutetrabenazine, an isotopic isomer of tetrabenazine, was also recently approved by the FDA as a treatment for tardive dyskinesia[97]. The impact of these new treatments is currently uncertain.

Most GABA agonists tested – including valproate, baclofen, progabide and tetrahydroisoxazolopyridine – have not shown any compelling benefit, and may worsen mental state[98]. However, clonazepam demonstrated moderate efficacy in one of the few double-blind randomized clinical trials for tardive dyskinesia[99]; tolerance developed to its antidyskinetic effect, but this could be restored by brief washout. Also of note, efficacy was more marked in those with primarily dystonic symptoms, as opposed to choreoathetoid dyskinesia.

A single fairly large randomized controlled trial found evidence that ginkgo biloba extract improved tardive dyskinesia symptoms and was well-tolerated[100]. This effect is possibly mediated by increases in BDNF[101]. Other supplement-based strategies include vitamin B6 (pyridoxal 5'-phosphate), with a recent meta-analysis providing weak but supportive evidence[102]. There is also weak evidence that vitamin E may protect against worsening of tardive dyskinesia, but this finding also requires further study[103].

A number of potential tardive dyskinesia treatments have very limited or conflicting evidence bases, including calcium channel blockers, other VMAT inhibitors such as reserpine, cholinergic and anticholinergic drugs, amantadine, and levetiracetam[104-106].

As a final resort, there is growing evidence that brain stimulation and surgical approaches may provide sustained relief of severe tardive dyskinesia, with particularly promising data for stimulation of the globus pallidus[107-109]. There have also been some case reports suggesting potential benefits of lesioning surgeries of the globus pallidus or thalamus[110].

Overall, a variety of treatment options exist for tardive dyskinesia but, with the exception of valbenazine and deutetrabenazine, none has met a level of clinical efficacy and safety sufficient to be approved by regulators. Prior to their development, the evidence-based guidelines of the American Academy of Neurology reported the strongest ("moderate") evidence of efficacy for clonazepam and ginkgo biloba[104].

Sialorrhea

Sialorrhea, the excessive production of saliva, is a side effect most commonly observed in patients treated with clozapine (possibly more than 90% of patients)[111], but can occur with other antipsychotics as well. It is believed to be related to actions on muscarinic and adrenergic receptors in the salivary glands[112,113]. It is often uncomfortable, embarrassing and stigmatizing, and can even result in aspiration pneumonia[114,115]. In some cases, painful swelling of the parotid can co-occur[116,117].

As with many antipsychotic side effects, using the lowest necessary dose and observing a gradual titration schedule are thought to minimize development of sialorrhea[118]. A number of treatments have been explored, principally antimuscarinic and alpha-adrenergic agents. Studies have focused almost exclusively on clozapine-induced sialorrhea[119], so the generalizability of findings to other antipsychotics is an open question.

Topical therapy with anticholinergics, typically by administering an ophthalmic or inhaler preparation sublingually, has been shown to improve symptoms. Atropine appears effective, though the short half-life limits its utility overnight[120-122]. Ipratropium has also shown good effect in several case studies [122-124], though a randomized controlled trial did not detect efficacy[125].

Among systemic antimuscarinic agents, there is evidence for efficacy of benztropine[21,126], trihexylphenidyl[127], glycopyrrolate[128], and pirenzepine[129,130]. Amitriptyline has also been tried in a small case series with promising results[131]. However, systemic antimuscarinic drugs present their own risks (confusion, blurred vision, constipation), which may be additive to clozapine's own anticholinergic effects.

Adrenergic agents also appear useful in antipsychotic-induced sialorrhea, though the mechanism is not clear. Clonidine has shown encouraging results in individual cases[132,133]. Another alpha-2 agonist, guanfacine, was effective in a single case[134]. The alpha-1 antagonist terazosin showed significant promise in a small trial[126], but has not subsequently been studied. Though these studies have not reported major side effects, the potential for worsening antipsychotic-induced orthostatic hypotension must be considered.

Several other pharmacologic strategies have been explored. The antipsychotics sulpiride and amisulpride have shown promising results in several small trials[135-137], as has the monoamine oxidase inhibitor moclobemide[136,138]. Finally, botulinum toxin injection has been shown to substantially improve antipsychotic-induced sialorrhea for 8-16 weeks[139,140].

If conservative, non-pharmacologic approaches are ineffective, we suggest that topical treatment with ipratropium or atropine be the initial approach to antipsychotic-induced sialorrhea, given the relative safety and tolerability. If these agents are ineffective, systemic medication can be used, selecting from the above-mentioned agents based on the patient's clinical picture (e.g., using clonidine in a patient with hypertension, benztropine in one with other extrapyramidal symptoms, amisulpride in one with resistant psychotic symptoms).

Sedation

All antipsychotic medications have been observed to cause sedation, but the severity and frequency vary widely among agents[141]. Sedation may be a causative factor in the increased risk for venous thromboembolism in patients treated with antipsychotics[142].

Although it is a common side effect and a frequently cited reason for medication non-adherence, the management of sedation has not been widely studied. Shifting dosing to nighttime, and reducing total daily dose, are the initially recommended approaches[143], followed by transitioning to a less sedating antipsychotic. Additionally, other sedating medications should be discontinued or changed when possible. The use of caffeine is also common, though it has not been systematically studied.

Stimulants and modafinil may improve cognitive and negative symptoms in schizophrenia[144], but relatively little research has focused on their potential utility in antipsychotic-induced sedation. In two cases, methylphenidate was reportedly useful and safe in treating patients with severe and unremitting sedation due to clozapine[145]. A small double-blind crossover study of methylphenidate did not specifically address antipsychotic-related sedation, but failed to find any benefit on a variety of clinical measures[146]. Moreover, methylphenidate has also been shown to worsen disorganization in patients with schizophrenia[147]. Likewise, despite case reports suggesting that modafinil may treat sedation[148], a systematic review of the literature found little or no evidence to support this[149], and a randomized controlled trial also found no significant effect[150]. A concern is that these medications may lead to worsening of movement disorders[151,152].

Prolactin, sexual function, and bone mineral density

Many antipsychotics can increase the release of prolactin, which can lead to a number of acute side effects: sexual dysfunction, anovulation, inappropriate lactation (galactorrhea), and gynecomastia. Antipsychotics can be imperfectly divided into prolactin-inducing and prolactin-sparing groups. The former include all first-generation antipsychotics, risperidone, paliperidone and amisulpride; the latter include clozapine, quetiapine, ziprasidone and aripiprazole[153]. Long-term hyperprolactinemia is also associated with decreased bone mineral density and osteoporosis[154].

Sexual dysfunction – including reduced libido, anorgasmia and erectile dysfunction – is common in patients taking antipsychotics[155,156] and must be monitored by prescribers. One measure to use is the Antipsychotics and Sexual Function Questionnaire[157]. Assessment of a patient with sexual dysfunction should include obtaining prolactin levels, reviewing other medications that may contribute, and ruling out potential comorbid causes[158]. Treatment strategies are largely dose reduction or switching to a prolactin-sparing antipsychotic (though sexual dysfunction is also common with clozapine and olanzapine)[159]. Evidence for specific symptom treatments (other than phosphodiesterase inhibitors for erectile dysfunction) is lacking[160].

Multiple studies have also identified an increased rate of osteopenia and osteoporosis in patients with schizophrenia[161,162]; however, multiple factors beyond antipsychotic use may contribute, including smoking, alcohol use, sedentary lifestyle, and poor nutrition[153]. Studies have shown that reduced bone mineral density and increased rate of hip fractures are associated with prolactin-inducing antipsychotics[163,164]. There has also been concern that elevated prolactin levels may be partly responsible for the observed increase in breast cancer rate among women with schizophrenia[165], though evidence is far from conclusive, due to multiple associated lifestyle and metabolic factors[166].

There is not yet a consensus on the appropriate monitoring for and management of hyperprolactinemia in people treated with antipsychotics[167-169]. In general, patients should be asked about baseline sexual dysfunction, menstrual irregularity and galactorrhea prior to initiation of antipsychotics. There is not a consensus on obtaining baseline prolactin levels. A conservative approach is to ask patients periodically about symptoms of hyperprolactinemia and to check the prolactin level in any patient developing symptoms. Another rational approach is to obtain a prolactin level at baseline and then approximately three months after starting an antipsychotic, as prolactin levels will have peaked by then[167].

Several specific populations are thought to be at particularly high risk for morbidity due to hyperprolactinemia and, if clinically feasible, should be placed on antipsychotics with minimal risk of raising prolactin levels[169]. First, in patients with established osteopenia or osteoporosis, a prolactin-sparing antipsychotic is obviously preferable. This may also apply to patients under the age of 25 who have not yet achieved peak bone mass, particularly women, who may be at increased risk for later osteoporosis[170]. Second, in female patients intending to become pregnant, a prolactin-sparing antipsychotic will be less likely to interfere with reproductive function. Third, and quite speculatively, in patients with a history of, or otherwise at elevated risk for breast cancer, there may be a greater danger of cancer or recurrence if treated with prolactin-elevating drugs[171].

Development of hyperprolactinemia in a patient on antipsychotics often presents a dilemma to the treating psychiatrist regarding further workup. If a baseline prolactin was obtained, and the elevation in prolactin appears clearly related to the antipsychotic, further workup is likely not necessary. More concerning signs include symptoms of pituitary disease (headaches, visual changes) and prolactin levels more than four times the upper limit of normal (>150 ng/mL), in which case evaluation by an endocrinologist and imaging (preferably magnetic resonance imaging) is warranted[167,169]. In cases of uncertainty (and where the risk of destabilizing the patient is low), a prolactin level assessment may be made after 3-4 days

off antipsychotics; a significant reduction in prolactin is reassuring that there is not an underlying pathology.

In cases of confirmed antipsychotic-induced hyperprolactinemia that are symptomatic, management is dose reduction or switch to a prolactin-sparing antipsychotic. If the clinical risk of dose reduction or switch is felt to be too high, an alternative strategy is to augment with aripiprazole, which has been shown to reduce prolactin levels in patients treated with risperidone[172]. A more experimental strategy is the use of dopamine agonists such as bromocriptine or cabergoline, which have been found to decrease prolactin and improve sexual function, though these may lead to worsening of psychotic symptoms[173,174].

An important but unanswered question is the role of bone density screening in patients on antipsychotics. The US Preventative Services Task Force recommends screening all women at age 65, while the US-based National Osteoporosis Foundation also recommends screening men over 70, as well as menopausal women with risk factors. Because individuals with schizophrenia often have multiple risk factors beyond antipsychotic use (e.g., smoking, obesity, diabetes), more aggressive screening is warranted than for the general population.

Orthostatic hypotension

All antipsychotics carry some risk of orthostatic hypotension, defined as a ≥20 mmHg drop in systolic or a ≥10 mmHg drop in diastolic blood pressure within three minutes of standing. Orthostatic hypotension can lead to dizziness, syncope, falls, and worsening of angina, and it should be evaluated by both history and measurement. Risk factors include systemic diseases causing autonomic instability (e.g., diabetes, alcohol dependence, Parkinson's disease), dehydration, drug-drug interactions, and age[175]. Chlorpromazine, sertindole, clozapine and quetiapine appear to have the greatest risk[176,177], and data suggest iloperidone is also high-risk[178]. Blockade of alpha-1 adrenoceptors and anticholinergic effects are believed to be the mechanism[179].

Switching to an antipsychotic that is rarely associated with orthostatic hypotension is a preferred management approach. Prevention of orthostatic hypotension relies on antipsychotic choice, gradual titration, and dosing distributed throughout the day (in order to minimize peak levels)[175]. Ample consumption of water and increased salt intake (supplementing 1-2 g/day), if not contraindicated, can reduce symptomatic hypotension[180]. Abdominal binders and leg compression stockings can reduce venous pooling and improve symptoms[181].

Pharmacologic treatment may be required in rare cases. Caffeine consumption may have a beneficial, mild pressor effect[180]. Fludrocortisone is widely used for treating orthostatic hypotension, and has been administered successfully in clozapine-associated orthostatic hypotension[182]; deleterious effects on blood sugar and electrolytes are a significant drawback, particularly in patients who already have metabolic side effects[175]. The alpha-1 agonist midodrine may also be considered[175,183], but has been linked to acute dystonias when combined with antipsychotics[184,185].

Sudden cardiac death and QT prolongation

Antipsychotics are associated with a 1.5 to 4-fold increase in risk of sudden cardiac death[186-189]. Risk factors include use of high dose or rapid administration, thioridazine or butyrophenone antipsychotics, and pre-existing hypertension or ischemic heart disease[188,190,191]. There are conflicting data for an association with age[188,192]. There is no evidence that second-generation antipsychotics are safer than first-generation drugs as a class[187].

The leading proposed mechanism is blockade of repolarizing potassium currents and prolongation of the QT interval, which are thought to lead to ventricular arrhythmias. Measurement of QT provides limited guidance in terms of risk; nevertheless, QTc >500 ms or an increase of 60 ms above baseline is regarded as a clear concern[193]. It is critical for the practitioner to consider all medications the patient is taking, as a diverse set of drugs cause QT prolongation[194]. A number of risk factors can make a modest QT prolongation dangerous, including bradycardia, hypokalemia, hypomagnesemia, congestive heart failure, atrial fibrillation, female gender, ion channel polymorphisms[194], and cocaine and chronic alcohol use[193].

Some experts argue that an electrocardiogram (ECG) should be obtained prior to, and shortly after, starting antipsychotic medications as a matter of course[195]. To support this view, they cite the significantly higher absolute risk of sudden cardiac death than clozapine-induced agranulocytosis, for which an extensive monitoring system is in place. Others recommend monitoring only with certain antipsychotics or when other risk factors are present[196]. The American Psychiatric Association's latest guidance recommends thorough physical exam and laboratory screening, with ECG indicated when thioridazine, ziprasidone, pimozide or mesoridazine are prescribed; family history of sudden cardiac death or long-QT syndrome are present; there is a personal history of syncope or known heart disease; or electrolyte abnormalities are present[197]. The UK National Health Service includes haloperidol, sertindole and pimozide as "high-risk" and requiring routine ECG, and recommends ECG if risk factors are present with "moderate-risk" drugs, including chlorpromazine, amisulpride, lurasidone, quetiapine, zotepine, promazine and melperone[198]. Patients who take more than one QT-prolonging drug warrant careful screening and monitoring.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome is one of the most dangerous adverse effects of antipsychotics. Hallmarks of the syndrome are fever, autonomic instability, rigidity and altered

mental status, associated with leukocytosis and elevated creatine phosphokinase. Mortality has been estimated at about 5%[199]. Neuroleptic malignant syndrome related to second-generation antipsychotics, particularly clozapine, may be less likely to present with signs of parkinsonism[200,201]. Incidence estimates vary widely, with the largest recent studies reporting rates of 0.02 to 0.04%[199,202,203]. The most important risk factor is a prior history of the syndrome. Pharmacologic risk factors include antipsychotic polypharmacy, high-potency antipsychotics, parenteral administration, rapid dose escalation, aripiprazole, lithium and benzodiazepine use[199,202,203]. Multiple medical comorbidities, heat exposure, dehydration, and the use of restraints are also associated with the syndrome[196,202-208].

Neuroleptic malignant syndrome is a medical emergency, often requiring intensive care. Evidence is from case reports rather than randomized clinical trials. For the psychiatrist, first steps are immediate withdrawal of all antipsychotics and related drugs (e.g., metoclopramide), cooling measures, and transfer to higher level of care[203]. Aggressive intravenous hydration and correction of electrolyte abnormalities are essential. Benzodiazepines may be helpful in treating the syndrome, and are preferable to physical restraint in agitated patients[200]. The skeletal muscle relaxant dantrolene and the D2-agonist bromocriptine are among first-line medications for moderate or severe neuroleptic malignant syndrome[199]. Electroconvulsive therapy has been successfully used in treatment-refractory cases[209].

Rechallenging a patient who has recovered from neuroleptic malignant syndrome with an antipsychotic is a clinical dilemma. The likelihood of recurrence is not well known, but likely in the range of 10-40%[210-212]. Longer delay from resolution of the syndrome to rechallenge is associated with reduced risk of recurrence[209]. In some cases, it may be necessary to treat a patient with electroconvulsive therapy to maintain symptom control for an extended period prior to rechallenge[213]. When reintroduction of an antipsychotic is necessary, it is prudent to select a drug with lower D2 potency (e.g., quetiapine or clozapine), pursue very gradual dose titration, and monitor closely.

Neutropenia/agranulocytosis

Neutropenia, the presence of too few infection-fighting neutrophils in the blood, and its extreme form, agranulocytosis, are most commonly associated with clozapine. These conditions and related increased susceptibility to infection are significant enough to warrant monitoring of granulocyte counts throughout a course of clozapine treatment. Clozapine has been associated with agranulocytosis ever since 16 cases, including eight deaths, were reported soon after the drug was introduced in Finland in 1975[214]. While many subsequent cases of clozapine-associated agranulocytosis have been reported[215], rare case reports with phenothiazines, including chlorpromazine, began appearing in the 1950s[216-218]. Case reports also implicate olanzapine[219] and risperidone[220]. About 3% of clozapine-treated patients will develop neutropenia; about 1% will develop agranulocytosis[221]. The risk for other antipsychotics is thought to be far lower.

The most important management strategy for neutropenia or agranulocytosis is early detection, which will prevent opportunistic infections. Because the period of highest risk is during the first months of treatment[215], neutrophil counts are measured more frequently in those months (weekly for 6 months in the US), then fortnightly for the remainder of the first year, and then monthly for the duration of treatment.

If neutropenia occurs, guidelines specify more frequent monitoring and when to interrupt treatment. For patients with stable but marginally adequate neutrophil counts, some clinicians use lithium to raise granulocyte counts above threshold levels to avoid increased monitoring requirements[222,223]. The mechanism by which lithium increases granulocyte counts is unknown[224].

Pharmaceutical versions of granulocyte colony-stimulating factor, a glycoprotein that induces bone marrow to produce and release granulocytes, may be used to treat agranulocytosis acutely[225,226]. For patients who have responded only to clozapine, such drugs may have a longer-term role in preventing agranulocytosis. For example, filgastram can be used over extended periods to maintain adequate neutrophil counts to avoid infections. Challenges for the use of filgastram include the need for parenteral administration and high cost.

Dose reduction is not an effective approach to clozapine-associated neutropenia[224]. Discontinuation of clozapine is the definitive solution to clozapine-induced neutropenia. This approach generally requires switching to another antipsychotic. For those patients who only responded to clozapine, clozapine re-challenge after agranulocytosis has not been successful, but case reports describe successful re-introduction of clozapine after neutropenia using either lithium or filgastram to increase neutrophil counts[227].

Behavioral addictions/impulse control disorders

Aripiprazole has been associated with the onset or exacerbation of impulse control disorders or behavioral addictions, including pathological gambling and compulsive eating, spending, shopping and sexual behaviors[228,229]. Because the dopamine agonists used to treat Parkinson's disease also cause impulse control disorders in a significant portion of patients, aripiprazole's partial dopamine agonist effect is presumed to be the mechanism[230-232]. Therefore, it is likely that other antipsychotics with dopamine agonist activity, such as cariprazine and brexpiprazole, may also have this effect.

The key to management of these compulsive behaviors is recognition that they are medication-induced and not simply part of an underlying mental or behavioral condition. In all reported cases, reducing the dose or discontinuing the causative medication was effective in ending the uncontrollable behav-

ior within weeks[228,233,234]. If an antipsychotic is necessary, one without dopamine agonist effects should be selected.

Myocarditis

Myocarditis, or inflammation of the heart muscle, is a rare but important medical risk of clozapine treatment that almost always occurs within the first two months of treatment[235,236]. Because myocarditis can progress quickly to cardiomyopathy and congestive heart failure, the best management strategy is to monitor for it, so that it can be recognized quickly. Slow titration may help[237,238]. At a minimum, patients initiating clozapine should be monitored weekly for signs and symptoms of myocarditis, including chest pain, dyspnea, orthopnea, peripheral edema, palpitations, fatigue, flu-like symptoms including fever, nausea and vomiting, and diaphoresis[239]. An ECG should be obtained and cardiac enzymes assessed as soon as myocarditis is suspected. Laboratory tests suggesting myocarditis in the context of recently started clozapine include elevated eosinophil count, C-reactive protein, sedimentation rate, and troponins. If myocarditis is suspected, an echocardiogram can assess ventricular and cardiac valve functioning; baseline echocardiograms are not necessary[239,240].

If a diagnosis of myocarditis is highly suspected or confirmed, then clozapine should be discontinued promptly, and general or specialty cardiac follow-up care is needed. In many cases cardiac function returns to normal after clozapine is stopped. Recurrence rates of clozapine-induced myocarditis are high; if the possible benefits of the drug are thought to justify this risk, it should be re-initiated in hospital with close monitoring[241].

Metabolic effects

Many antipsychotic medications are associated, to variable degrees, with weight gain, hypertension, and adverse effects on lipid and glucose metabolism.

Several antipsychotics are associated with significant weight gain, and virtually all antipsychotics are known to cause weight gain among youth[3]. Weight gain is among the most important antipsychotic side effects, because it is distressing to individuals and increases the risk of adverse health outcomes such as degenerative joint disease, type 2 diabetes mellitus and its complications, cardiovascular and cerebrovascular disease, as well as some types of cancer, and liver and kidney disease. Although weight gain commonly accompanies other adverse metabolic effects, adverse changes in lipids and insulin sensitivity may occur independently of weight gain[3].

Anyone taking an antipsychotic medication should be regularly monitored for metabolic side effects. If these effects occur, lifestyle modifications are widely recommended and are a reasonable first step for individuals taking antipsychotic medications. Several structured behavioral programs have been tested and found effective in individuals with severe mental illnesses[242-245]. Switching to an antipsychotic with lower risk for metabolic problems can be effective in helping individuals to lose weight and improve metabolic profiles[4,5].

Metabolic problems that develop in the context of successful antipsychotic treatment can also be treated symptomatically, as they are in the general population. For example, statins are used to treat dyslipidemias, and antihypertensive medications are used to treat hypertension. Metformin has repeatedly been shown in randomized controlled trials to be modestly effective in helping patients taking antipsychotics to lose weight, even if the weight gain was not recent[246-249]. Recently approved weight loss drugs – including lorcaserin, bupropion/naltrexone, and liraglutide – have not been tested specifically for antipsychotic-induced weight gain. Preliminary data on naltrexone alone suggests that it may be helpful[250]. Stimulant weight loss medications are not recommended due to their psychotogenic potential.

Anticholinergic effects

Anticholinergic side effects of antipsychotics include decreased salivation leading to dry mouth, decreased intestinal mobility leading to constipation, inhibition of visual accommodation leading to blurred vision, increased pupil size, and tachycardia[251]. These effects may lead to medical complications such as dental caries, ileus, and angina or myocardial infarction. Because increased pupil size can exacerbate narrow-angle glaucoma, this condition should be treated before initiating antipsychotic treatment; an antipsychotic with minimal anticholinergic effects should be selected. Similarly, prostatic hypertrophy should be treated and an antipsychotic with little anticholinergic effect should be used[251].

Decreasing the antipsychotic dose is the first-choice management strategy for anticholinergic side effects. Changing to a medicine with less anticholinergic effects may also be effective[251]. Finally, symptomatic management is a reasonable approach, but there is little evidence specific to antipsychotic-induced anticholinergic effects.

Constipation due to antipsychotics, particularly clozapine, can be severe and can lead to ileus[252,253]. Prevention and early recognition are critical. Recommended management strategies include adequate hydration; use of osmotic agents such as sorbitol, lactulose, or polyethylene glycol, and stimulant laxatives such as senna or bisacodyl. The benefits of stool softeners such as docusate sodium are unclear[4]. Bulk-forming, fiber-based laxatives are generally not recommended for slow-transit constipation such as that caused by anticholinergic effects[254].

CONCLUSIONS

The considerable benefits of antipsychotic medications are countered, to some extent, by their adverse effects. Appropri-

ate prevention and early management of these effects can enhance the net benefits of antipsychotics. Our review found that, in general, few management approaches are supported by strong empirical evidence; recommendations are often based at least in part on expert opinion.

Nevertheless, a few key principles apply broadly. Only use antipsychotics if the indication is clear; only continue antipsychotics if a benefit is discernible. If an antipsychotic is providing substantial benefit, and the adverse effect is not life-threatening, then the first management choice is to lower the dose or adjust the dosing schedule. Next is to change the antipsychotic; this is often reasonable unless the risk of relapse is high, such as when an individual has only responded to clozapine. In some instances, behavioral interventions can be tried. Finally, concomitant medications, though generally not desirable, are necessary in many instances.

Evidence suggests that adverse effects are not the main reason why individuals discontinue an antipsychotic medication[255]. Nevertheless, optimal management of adverse effects will improve patients' quality of life and their functional outcomes.

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