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REVIEW

Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review

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Marco Solmi,[1,2] Andrea Murru,[3] Isabella Pacchiarotti,[3] Juan Undurraga,[4,5] Nicola Veronese,[2,6] Michele Fornaro,[7,8] Brendon Stubbs,[2,9–11] Francesco Monaco,[2] Eduard Vieta,[3] Mary V Seeman,[12] Christoph U Correll,[13,14] André F Carvalho[2,15]

[1]Neuroscience Department, University of Padua, [2]Institute for Clinical Research and Education in Medicine, Padua, Italy; [3]Bipolar Disorders Unit, Institute of Neuroscience, Hospital Clínic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain; [4]Department of Psychiatry, Faculty of Medicine, Clínica Alemana Universidad del Desarrollo, [5]Early Intervention Program, J. Horwitz Psychiatric Institute, Santiago, Chile; [6]National Research Council, Ageing Section, Padua, [7]Laboratory of Molecular and Translational Psychiatry, Department of Neuroscience, School of Medicine, University "Federico II", Naples, Italy; [8]New York State Psychiatric Institute, Columbia University, New York, NY, USA; [9]Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, [10]Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, [11]Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford, UK; [12]Institute of Medical Science, Toronto, ON, Canada; [13]Department of Psychiatry Research, Zucker Hillside Hospital, Northwell Health, Glen Oaks, [14]Department of Psychiatry and Molecular Medicine Hempstead, Hofstra Northwell School of Medicine, Hempstead, NY, USA; [15]Translational Psychiatry Research Group and Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil

Correspondence: André F Carvalho
Translational Psychiatry Research Group and Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceará, Rua Professor Costa Mendes, 1608 – 4° andar, 60430-140 Fortaleza, Ceará, Brazil
Fax +55 85 3366 8054
Email andrefc7@hotmail.com

Abstract: Since the discovery of chlorpromazine (CPZ) in 1952, first-generation antipsychotics (FGAs) have revolutionized psychiatric care in terms of facilitating discharge from hospital and enabling large numbers of patients with severe mental illness (SMI) to be treated in the community. Second-generation antipsychotics (SGAs) ushered in a progressive shift from the paternalistic management of SMI symptoms to a patient-centered approach, which emphasized targets important to patients – psychosocial functioning, quality of life, and recovery. These drugs are no longer limited to specific *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) categories. Evidence indicates that SGAs show an improved safety and tolerability profile compared with FGAs. The incidence of treatment-emergent extrapyramidal side effects is lower, and there is less impairment of cognitive function and treatment-related negative symptoms. However, treatment with SGAs has been associated with a wide range of untoward effects, among which treatment-emergent weight gain and metabolic abnormalities are of notable concern. The present clinical review aims to summarize the safety and tolerability profile of selected FGAs and SGAs and to link treatment-related adverse effects to the pharmacodynamic profile of each drug. Evidence, predominantly derived from systematic reviews, meta-analyses, and clinical trials of the drugs amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, CPZ, haloperidol, loxapine, and perphenazine, is summarized. In addition, the safety and tolerability profiles of antipsychotics are discussed in the context of the "behavioral toxicity" conceptual framework, which considers the longitudinal course and the clinical and therapeutic consequences of treatment-emergent side effects. In SMI, SGAs with safer metabolic profiles should ideally be prescribed first. However, alongside with safety, efficacy should also be considered on a patient-tailored basis.

Keywords: antipsychotics, side effects, tolerability, safety, psychosis, psychiatry

Introduction

Severe mental illness (SMI), including major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia spectrum disorders, represents a major public health issue, accounting for significant health and social and economic burden worldwide.[1–5] The chronic nature of SMI is characterized by recurring episodes,[6,7] residual symptom burden, and a variable degree of cognitive dysfunction and functional impairment, which may persist even during periods of remission.[8–13] In addition, growing evidence indicates that acute, and especially chronic, manifestations are only partially addressed with first-line, approved treatments.[14] More recently, the use of atypical or second-generation antipsychotics (SGAs) has been extended to cover a wide

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range of psychiatric conditions besides schizophrenia and schizoaffective disorders. They have become especially popular as add-on treatment for patients with MDD who fail to adequately respond to antidepressants,[15] for BD,[16–18] and for behavioral symptoms associated with dementia.[19,20] In addition, systematic evidence and meta-analysis indicate that SGAs are frequently used for several off-label indications;[21,22] they have been advocated as "multidimensional" agents.[23]

Since the serendipitous discovery of chlorpromazine (CPZ) for psychosis in 1952, first-generation antipsychotics (FGAs) have revolutionized psychiatric care, leading to across-the-board discharges from long-stay institutions and marked reductions in hospitalization rates.[24] Until the 1950s, patients suffering from SMI often required prolonged hospitalization, sometimes lifetime institutionalization, and were offered remedies with little or no evidence of benefit. The situation improved upon the development of FGAs, which allowed for safe and effective treatment in the community.[25] The introduction of FGAs led to good control of behavioral and symptomatic domains in SMI (especially true for "positive" symptoms such as delusions and hallucination), due to a heterogenous combination of strong D2 blockade and anticholinergic and antihistaminergic actions.[26,27] Yet, this success turned out to be only partial because FGAs did not help and often had a deleterious impact on negative, cognitive, affective, and/or motor domains.[28] With the rediscovery of clozapine (CLO),[29,30] SGAs, which combined potent (5HT2A) serotonergic blockade with potent but "fast-off" dopamine D2 blockade, were developed. The range of therapeutic indications was broadened, and there was a progressive shift from a paternalistic behavioral control of SMI symptoms to a more patient-centered approach, which valued improved psychosocial functioning and quality of life.[31–33] Since the early 2000s, the development of antipsychotics with partial agonism at dopamine D2 receptors has led several authors to speak of a class of "third-generation" antipsychotics.[34] However, the lack of a third neuroreceptor system related to efficacy has for the most part prevented the widespread adoption of this terminology. Compared to the pharmacodynamic profile of FGAs, that of SGAs has a less specific antagonistic action at the D2 receptor and often a relatively stronger serotonin 5HT2A receptor action, as well as variable alpha adrenergic, antihistaminergic, and anticholinergic activities, plus exhibits a varying affinity at other (sub-) receptor types.[35] Over the past 20 years, the main tolerability concerns have shifted from the sometimes disabling and always stigmatizing extrapyramidal adverse effects of FGAs to cardiometabolic issues that affect health and life span and are associated – to varying degrees – with SGAs.[35–39]

Despite the widespread use of SGAs, many concerns have been raised regarding their safety and tolerability. Safety issues vary according to patient populations and across various compounds. For example, the appropriateness of SGA use has been debated in patients with dementia due to an increased incidence of cerebrovascular events and death compared to placebo.[21,40] Furthermore, different SGAs differentially induce treatment-emergent weight gain and metabolic disturbances,[41] among other side effects, thus affecting drug tolerability and safety[36,42] to different degrees. Given that these drugs usually need to be taken indefinitely, tolerability[43] and treatment adherence,[44,45] and their relationship to outcomes in SMI,[46] must always be considered alongside with efficacy.

Hence, the main objective of this review is to critically review the literature in order to provide clinically oriented state-of-the-art coverage of the safety and tolerability profile of selected FGAs and SGAs in SMI. The secondary objective is to provide a succinct overview of possible pharmacological mechanisms underpinning differences in tolerability and safety among SGAs and to interpret tolerability data according to the "behavioral toxicity" framework.[47–49] This refers to treatment-induced alterations in mood, perception, cognition, and psychomotor function, all of which can potentially worsen illness course.[50] Importantly, some of these untoward effects may persist long after drug discontinuation.[50,51] Such phenomena are captured by the term iatrogenic comorbidity,[50,51] a negative outcome of the treatment of psychosis whose unfortunate pervasiveness is this review hopes to reduce.

Methods

This is a narrative review of selected side effects (Table 1) based on a PubMed/MEDLINE database search on December 20, 2016, using the following search terms: "second-generation antipsychotic" OR "SGA*" OR "atypical antipsychotic" cross-referenced with "drug-related side effects and adverse reactions" [Mesh] OR "specific side effects" (Table 1), without publication date or language limit. We synthesized the evidence in a best evidence synthesis and considered large-scale observational studies, randomized controlled trials (RCTs), previous meta-analyses, or systematic reviews (SRs), and single-drug package insert data as well. When none of the former options were available, we also considered case reports for preliminary emerging evidence not otherwise covered in the literature.

Table 1 Main treatment-emergent adverse events related to the use of antipsychotics

Adverse effects and behavioral toxicity of antipsychotics at therapeutic doses
Sedation
Cognitive impairment
Weight gain and obesity
Metabolic syndrome and its components (waist circumference, dyslipidemia, high fasting blood sugar, diabetes mellitus, and hypertension)
Neuromotor adverse effects (EPS, bradykinesia, dystonia, akathisia, and TD)
Seizures
QTc prolongation, HRV, and SCD
Hypotension
Myocarditis and cardiomyopathy
Coronary heart disease and stroke
Pneumonia and acute respiratory failure
Pulmonary embolism and venous thromboembolism
Gastrointestinal adverse effects (eg, nausea, vomiting, diarrhea, and constipation)
Dry mouth, sialorrhea, and dental caries
Liver toxicity
Urinary and kidney dysfunction
Leucocytopenia, agranulocytosis, and thrombocytopenia
Osteopenia, osteoporosis, and fractures
Falls
Binge eating, impulse discontrol, and gambling
Tobacco use and smoking
Sexual and reproductive system dysfunction
Endocrine adverse effects (diabetes ketoacidosis, hypothyroidism, and hyponatremia)
Hyperprolactinemia and prolactinoma
Breast and cervical cancers
Malignant neuroleptic syndrome
Use in pregnancy and breastfeeding
Withdrawal syndromes
Rebound syndromes

Abbreviations: EPS, extrapyramidal symptoms; TD, tardive dyskinesia; HRV, heart rate variability; SCD, sudden cardiac death.

Adverse effects and behavioral toxicity related to antipsychotic use

Table 2 summarizes the selected pharmacodynamic receptor profile of several FGAs and all marketed SGAs in Europe and the US. A detailed overview of drug specific tolerability and safety profiles is reported in Table 3. We considered selected FGAs (CPZ, haloperidol (HAL), loxapine [LOX], molindone [MOL], and perphenazine [PER]) and the SGAs amisulpride (AMI), aripiprazole (ARI), asenapine (ASE), brexpiprazole (BRE), cariprazine (CAR), CLO, iloperidone (ILO), lurasidone (LUR), olanzapine (OLA), paliperidone (PALI), risperidone (RIS), quetiapine (QUE), sertindole (SER), and ziprasidone (ZIP).

Sedation

Sedation can be a therapeutic target in the acute treatment of SMI patients presenting with agitation or severe behavioral symptoms but is also a safety concern and should be avoided in the long-term treatment due to its relationship with adverse effects on cognitive performance, physical activity/sedentary behavior/body weight, and patients' satisfaction with therapy, among others, as shown in an influential meta-analysis and randomized clinical trials.[28,52] Sedation is linked with the blockade of histaminergic receptors and is highest for CLO, zotepine, and CPZ, gradually decreasing from QUE, OLA, ZIP, ASE, HAL, and RIS to LUR, ARI, ILO, SER, PALI, and AMI, as shown in a comparative meta-analysis of trials of acute antipsychotic use in schizophrenia.[28] Rather than being sedative, CAR shows an activating profile according to its high number in a number needed to harm trial.[53] In BD, a recent meta-analysis showed surprisingly comparable sedation between ARI and other SGAs,[54] which may be an artifact due to frequent benzodiazepine coadministration in the beginning of trials in acute BD mania or may be associated with ARI itself, particularly at doses >20 mg/day.

Cognitive impairment

FGAs and SGAs can both impair cognitive functions in the first-episode schizophrenia, with the former being linked to a worse profile, as shown in a meta-analysis.[55] The cognitive effect of antipsychotics is a complex domain, which can be influenced by baseline cognitive ability,[56] plus anxiety, mood, positive, negative, and residual symptoms in patients with schizophrenia. Considered as a unique domain, cognitive performance is negatively influenced by high doses of drugs with strong anticholinergic properties and with strong D_2 blockade in patients with schizophrenia, as shown by several RCTs.[57,58] Consequently, while RIS and HAL can impair cognitive function through a decrease in dopamine transmission, CLO, OLA, and QUE exert similar effects perhaps through more potent anticholinergic activity and also because they are potent D2 blockers in their own right (but for shorter periods of time). Moreover, it is not clear whether coadministration of anticholinergic drugs for extrapyramidal symptoms (EPS) and dampening of motivation may confound net effect of antipsychotics on cognition. Since cognitive function benefits indirectly from an improvement in hallucinations and thought disorganization[59] due to antipsychotic administration, the net effect on cognition is often null, as reported in RCTs and SRs.[60,61] However, cognition is frequently reported only as a secondary outcome, or not reported at all, as shown in SRs of RCTs of SGAs in schizophrenia.[62,63] It has been hoped

Table 2 Neuroreceptor binding profiles of antipsychotics

Drug	K_i D2	K_i 5HT1A	K_i 5HT2A	K_i 5HT2C	K_i α1	K_i α2	K_i H1	K_i M2
CPZ	*3*	*2,115*	*4.06*	*32.5*	*2.6*	*750*	*3*	*244*
HAL	*2.6*	*1,800*	*61*	*4,700*	*17*	*600*	*260*	*>10,000*
LOX	*9.8*	*NA*	*2*	*NA*	*250*	*NA*	*14.9*	*NA*
MOL	*120*	*3,797*	*5,000*	*>10,000*	*2,500*	*625*	*>10,000*	*NA*
PER	*1.4*	*421*	*5*	*132*	*10*	*500*	*8*	*NA*
AMI	1.3	>10,000	2,000	>10,000	7,100	1,600	>10,000	NA
ARI	±0.7	±5.5	8.7	22	26	74	30	3,510
ASE	1.3	2.5	0.06	0.03	1.2	1.2	1	>10,000
BRE	±0.3	±0.12	0.47	NA	3.8	0.59	19	NA
CAR	±0.5	±2.6	18.8	134	155	NA	23.2	>10,000
CLO	210	160	2.59	4.8	6.8	158	3.1	204
ILO	6.3	168	5.6	14	4.7	4.7	437	3,311
LUR	1	±6.4	0.5	NA	NA	11	>10,000	>10,000
OLA	20	610	1.5	4.1	44	280	0.1	622
PALI	2.8	480	1.2	48	10	80	3.4	>10,000
RIS	3.8	190	0.1	32	2.7	8	5.2	>10,000
QUE	770	300	31	3,500	8.1	80	19	630
SER	2.7	2,200	0.14	6	3.9	190	440	NA
ZIP	4.8	±3.4	0.4	1.3	10	154	4.6	>3,000
Effects related to receptor blockade								
	EPS, hyperprolactinemia, sexual dysfunction, and cognitive dysfunction	Anxiolytic and antidepressant effects	Lower incidence of akathisia and parkinsonism	Weight gain and metabolic effects	Hypotension, priapism, retrograde ejaculation, and low libido	Antidepressant	Appetite, sedation, cognitive dysfunction, and weight gain	Cognitive dysfunction, urinary retention, glaucoma, constipation, and dry mouth

Notes: Lower K_i (ie, nanomolar concentration at which 50% of the respective receptor type is occupied) means higher affinity. Light gray, FGAs; ±, partial agonism for the specific receptor. Italics represent FGAs. Data from Correll.[35]

Abbreviations: CPZ, chlorpromazine; HAL, haloperidol; LOX, loxapine; NA, not applicable; MOL, molindone; PER, perphenazine; AMI, amisulpride; ARI, aripiprazole; ASE, asenapine; BRE, brexpiprazole; CAR, cariprazine; CLO, clozapine; ILO, iloperidone; LUR, lurasidone; OLA, olanzapine; PALI, paliperidone; RIS, risperidone; QUE, quetiapine; SER, sertindole; ZIP, ziprasidone; EPS, extrapyramidal symptoms; FGAs, first-generation antipsychotics; FGA, first-generation antipsychotics.

that ARI would, unlike other antipsychotic drugs, improve cognition. The drug may ameliorate pre-attentive functions,[64] possibly due to both its partial D2 agonism and its almost absent affinity to cholinergic receptors. However, clinical data from RCTs do not seem to confirm such a priori expectations, as they show no change in cognitive function when ARI or BRE are administered to patients with schizophrenia.[65] Furthermore, no difference in effects on cognitive function emerged when ARI was meta-analytically compared with other antipsychotics in schizophrenia.[66]

Weight gain and obesity

Although most high-potency FGAs have relatively little weight gain potential, low-potency FGAs and most SGAs can substantially increase the risk of weight gain and ultimately of obesity in schizophrenia.[36,42,67] However, the weight gain potential differs substantially among SGAs, and certain FGAs can even induce more weight gain than specific SGAs. In particular, while HAL, ZIP, LUR, ARI, BRE, CAR and AMI are associated with little weight gain, at least in chronic patients who are often already overweight, PALI, RIS, and QUE induce moderate weight gain, SER, CPZ, ILO, strongly increase body weight, with extreme body mass index (BMI) increases with treatment by CLO, zotepine, and OLA.[28,68] There seems to be less consensus regarding ASE, which has been described by different SRs as either one of the SGAs with least weight gain[28] or as a weight neutral drug[68] in schizophrenia. In any case, all antipsychotics are associated with often substantial weight gain, especially evident when treating antipsychotic-naïve patients.[69,70]

Metabolic syndrome and its components (waist circumference, dyslipidemia, diabetes mellitus, and hypertension)

Metabolic syndrome is defined by the presence of three or more of five criteria, including increased waist circumference (central obesity), elevated blood pressure, low high-density lipoprotein cholesterol, hypertriglyceridemia, and hyperglycemia.[71] Since patients with metabolic syndrome are at an increased risk of cardiovascular disease (CVD),[71] drugs with a more favorable metabolic profile are preferred in BD and schizophrenia.[36] Antipsychotics can directly or

Table 3 Adverse effect profiles of selected FGA and SGA drugs[#]

Adverse effect	Mechanism	Dose/titration dependent	AMI	ARI	ASE	BRE	CAR	CLO	ILO	LUR	OLA	PALI	QUE	RIS	SER	ZIP	*CPZ*	*HAL*	*LOX*	*PER*
Sedation	H1 blockade	+++	0/+	0/+	+	0/+	0/+	+++	0/+	+/++	+/++	0/+	++	+	0/+	+	+++	+	+	+
Cognitive impairment	Anticholinergic, D2 blockade	++	+	0	+	0	0	+	0	0	+	+	+	+	+	0	++	++	++	++
Weight gain	H1, D2, 5HT2c blockade	0/+	0/+	0	+	0	0/+	+++	+/++	0/+	+++	++	++	++	++	0/+	+++	+	+	++
Metabolic syndrome	Weight gain, overeating, direct effects	0/+	0/+	0/+	0/+	0/+	0/+	+++	+	0/+	+++	+	++	+	+	0/+	+++	*0/+*	+	+
Acute parkinsonism	D2 blockade	+++	+	+	++	+	++	0	0/+	++	0/+	++	0	++	0/+	+	+	+++	++	++
Akathisia	D2 blockade and α, 5HT interaction	+++	+	++	+	++	++	+	0/+	+/++	+	+	+	++	+	+/++	+	+++	++	++
TD	D2 receptor desensitization	++	0/+	0/+	0/+	0/+	0/+	0	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	++	+++	++	++
Withdrawal dyskinesia	D2 blockade rebound	+++	+	+/++	+	+/++	+/++	0	+	+	0/+	+	0/+	+	0/+	+	*0/+*	++	+/++	+/++
Seizures	D2 blockade	+++	0/+	0/+	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+	+	0/+	0/+	*0/+*	*0/+*	*0/+*	*0/+*
Increase in QTc interval	Cardiac ion channel effects	++	++	0	+	0	0	+	0/+	0/+	+	+	+	++	++	++	+	++	+	+
Hypotension	α1 blockade	+++	0/+	0/+	+	0/+	0/+	+++	+++	0/+	++	+	++	++	+	++	+++	++	+	++
Cardiovascular events (myocardial infarction and stroke)	Hypercoagulability, metabolic effects, direct channel toxic action	+	0/+	0/+	+	0/+	?	++	?	?	++	+	++	++	0/+	+	++	++	+	++
Sialorrhea	M4 agonism	+	0	0	0	0	0	++	0	0	0	0	0	0	0	0	*0*	*0*	*0*	*0*
Neutropenia	Direct effect	+	0/+	0/+	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	+	*0/+*	*0/+*	*0/+*
Increase in prolactin/sexual dysfunction	D2 blockade	+++	+++	0	+	0	0	0	0/+	+	+	+++	0	+++	+	+	+	++/+++	++	++
Myocarditis and cardiomyopathy	Unknown	0	0	0	0	0	0	++	0	0	0	0	0/+	0	0	0	*0*	*0*	*0*	*0*
Pneumonia and acute respiratory failure	Sialorrhea, central sedation, muscle impairment	+++	+	0	0	0/+	0/+	++	0/+	0/+	+	0/+	0/+	+	0/+	0	+	+	+	+
Gastrointestinal adverse effects (eg, nausea, vomiting, diarrhea, and constipation)	Anticholinergic, D2 agonism	+	0	+	0	+	+	++	0	0	++	0	0	0	0	0	++	*0*	++	++
Pulmonary embolism and venous thromboembolism	Hypercoagulability	0/+	+	0/+	+	?	?	+	?	?	+	+	+	+	0/+	0/+	++	+	+	++
Dry mouth and dental caries	Anticholinergic	+	0	0	0	0	0	++	0	0	++	0	++	0	0	0	++		++	++
Liver dysfunction	Metabolic syndrome, direct effect	0/+	0/+	0/+	0/+	0/+	0/+	++	0/+	0/+	+	0	+	+	0/+	0	++	*0/+*	*0/+*	*0/+*
Urinary and kidney functions	Anticholinergic (prolactin)	++	+	0	0	0	+	+	0	+	+	0	0	0/+	0	0/+	+	*0*	*0*	+
Osteopenia, osteoporosis, and fractures	D2 blockade (prolactin)	+	+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	+	0/+	+	0/+	0/+	*0/+*	+	*0/+*	*0/+*
Binge eating, impulse control disorder, and gambling	H1 blockade, D2 agonism	+	0	+	+	?	?	++	0	0	++	+	0	+	0	0/+	+	*0*	*0*	*0*
Sexual and reproductive system dysfunction	D2 blockade (prolactin), α blockade, anticholinergic	++	+	0/+	+	?	0	++	?	+	++	++	+	++	+	0/+	++	++	++	++

(*Continued*)

Table 3 (*Continued*)

Adverse effect	Mechanism	Dose/titration dependent	AMI	ARI	ASE	BRE	CAR	CLO	ILO	LUR	OLA	PALI	QUE	RIS	SER	ZIP	*CPZ*	*HAL*	*LOX*	*PER*
Endocrine adverse effects (diabetes, ketoacidosis, hypothyroidism, and hyponatremia)	Unknown	0/+	0/+	0/+	0/+	0/+	0/+	++	0/+	0/+	++	0/+	0/+	++	0/+	0/+	*0/+*	*0/+*	*0/+*	*0/+*
Hyperprolactinemia	D2 blockade	+++	+++	0	+	0	0	+	+	++	+	+++		+++	++	++	+	*+++*	+	+
Breast and cervical cancers	Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	*0*	*0*	*0*	*0*
Malignant neuroleptic syndrome	Unknown	++	0/+	0/+	0/+	?	?	+++	?	?	+	0/+	+	+	+	+	*+++*	*+++*	+	+

Notes: +, ++, and +++ indicate comparative, not absolute, and side effect relevance among drugs. ? indicates no evidence available. Italics represent FGAs.

Abbreviations: FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; AMI, amisulpride; ARI, aripiprazole; ASE, asenapine; BRE, brexpiprazole; CAR, cariprazine; CLO, clozapine; ILO, iloperidone; LUR, lurasidone; OLA, olanzapine; PALI, paliperidone; QUE, quetiapine; RIS, risperidone; SER, sertindole; ZIP, ziprasidone; CPZ, chlorpromazine; HAL, haloperidol; LOX, loxapine; PER, perphenazine; TD, tardive dyskinesia; FGA, first-generation antipsychotics.

indirectly adversely affect cardiometabolic health in various ways, ranging from increasing appetite and food intake[72] to a more sedentary lifestyle linked to sedation or EPS;[73] however, it has been shown that cardiometabolic adverse effects of antipsychotics are to some degree independent of lifestyle parameters.[74] Polypharmacotherapy increases the risk of metabolic syndrome.[38] A meta-analysis showed that both FGAs and SGAs increase the risk of metabolic syndrome compared to a no drug condition in SMI.[36] According to the same meta-analysis and individual studies, the metabolic liability of antipsychotics ranges broadly, the lowest risk associated with ARI, BRE, CAR, LUR, ZIP, and high-potency FGAs (HAL) and the highest risk associated with CPZ, CLO, OLA, and QUE. All other antipsychotics are considered as having a medium/intermediary risk.[36] Longer term data are still lacking with the newest SGAs, BRE, and CAR.

Neuromotor side effects (EPS, bradykinesia, dystonia, akathisia, and tardive dyskinesia)

EPS, including bradykinesia, muscle rigidity, tremor, dystonia, akathisia, and tardive dyskinesia (TD), are linked to the ratio of D_2 receptor to 5HT2A receptor binding. According to several meta-analyses,[28,75] the highest incidence of EPS in patients with schizophrenia occurs with HAL, with moderate EPS being observed with RIS, PALI, and LUR, down to CPZ; milder EPS being observed with ASE, ZIP, AMI, ILO, and ARI; and still milder EPS being observed with QUE, OLA, SER, and CLO. Although CAR is a partial D2 agonist, it seems to increase the risk of EPS according to a recent meta-analysis across SMI,[76] perhaps due to relatively weak 5HT2A antagonism (or more antagonism than agonism). Perhaps because of illness-induced serotonin disturbance, BD patients, especially in depression, have been found in one meta-analysis to be more vulnerable to acute movement disorders secondary to antipsychotics than patients with schizophrenia.[77]

Akathisia, defined as a compelling need for constant motion, associated with marching up and down, crossing and uncrossing the legs when sitting, and improving after drug dose reduction or coadministration of benzodiazepines, should be differentiated from pseudoakathisia.[78,79] The latter is characterized by inner restlessness as a sign of pharmacodynamic or pharmacokinetic rebound-induced restlessness and improves when the dose of an antipsychotic is increased. Akathisia can occur with both FGAs and SGAs, but FGAs are more likely to produce clinically relevant akathisia as per one meta-analysis.[55] Comparative meta-analyses show

that ARI induces more akathisia than OLA in schizophrenia and BD, CLO and RIS more than ZIP, and RIS more than SER.[54,75] It should be noted that some overlap between akathisia and pseudo-akathisia labeling may have influenced these results.

Compared to FGAs, an up to sixfold lower incidence of TD, tardive dystonia, and tardive akathisia occurs with SGAs in schizophrenia.[80,81] Some evidence pointed to a possible increased risk for TD in populations with BD.[82] Nonetheless, data on the incidence of TD in BD are substantially lacking or else are totally missing as in the case of long-acting depot RIS.[83] ARI has been associated with TD, in particular when high doses are prescribed, in female elderly patients in particular.[84]

While an association between some genetic polymorphisms[85,86] and TD has been described in patients with schizophrenia, there is no consensus about a genetic predisposition to TD.[87] On the other hand, several clinical variables have consistently predicted TD occurrence in schizophrenia in observational studies, RCTs, and reviews; these include anticholinergic medication; older age; intermittent antipsychotic treatment; high cumulative dose; higher negative, cognitive, and affective symptoms; and early movement side effects.[88–91] At present, no specific SGA can be considered as conferring a higher TD risk than others in schizophrenia.[92]

Seizures

A World Health Organization (WHO) adverse drugs reaction database study hypothesized a higher risk for seizures not only with SGAs than FGAs, especially with CLO, but also with OLA and QUE.[93] Yet, this contrasts with the results of a recent meta-analysis finding a slightly increased risk for seizures with FGAs compared to SGAs. Still, CLO seems associated with a higher seizure risk in patients with either BD or schizophrenia compared to other SGAs.[94,95] One population-based study reported an increased risk of antipsychotic-related seizures with CLO and HAL, finding a lower risk with ARI compared with RIS. Clinical variables, such as younger age, a diagnosis of schizophrenia versus BD, and higher antipsychotic doses may help to identify subpopulations at higher risk for treatment-emergent seizures, but no causal inference can be made based on cross-sectional data.[95] While a precise mechanism is unknown, a role of D2 and D3 receptors has been suggested.[96]

QTc prolongation, heart rate variability, and sudden cardiac death

Patients with schizophrenia have shown a proneness to rhythm alterations, such as Brugada syndrome.[97] In addition to such a predisposition, cardiac electrical activity can be altered by antipsychotic use, resulting in QTc prolongation, even in younger patients, in particular in women.[98,99] In adults, QTc prolongation is generally clinically relevant when QTc is >500 milliseconds or when QTc increases by ≥60 milliseconds from drug-free baseline,[39] resulting in an increased risk of torsades de pointes and sudden cardiac death (SCD). QTc alterations may start as early as 2 weeks after the beginning of antipsychotic treatment in the first-episode schizophrenic patients.[100] In a recent, nationwide study, use of any antipsychotics was associated with a 1.5-fold increased risk of ventricular arrhythmia and/or SCD, being somewhat higher with FGAs (odds ratio [OR] =1.66, 95% CI 1.43–1.91) than with SGAs (OR =1.36, 95% CI 1.20–1.54),[101] with an increased risk of up to 5.8-fold, depending on the definition of SCD.[39]

In an observational study of patients with BD, SGAs were shown to decrease heart rate variability (HRV), in particular those drugs with high affinity for the D2 receptor.[102] Since HRV is a recognized predictor of SCD, routine monitoring of HRV may help in identifying at-risk subjects and possibly prevent SCD.[103] According to several meta-analyses and individual studies on schizophrenia, ARI, BRE, CAR, and ILO do not seem to have a clinically relevant effect on QT in schizophrenia, whereas ASE, CLO, OLA, and QUE may have a moderate effect, and finally, AMI, PALI, RIS, ZIP, and SER as well as thioridazine have been associated with the highest QT prolongation.[28,104–106]

Hypotension

Hypotension is a relevant side effect, which can be complicated with syncope. Falls sometimes lead to hip fracture, transient ischemic attacks, myocardial infarction in rare occasions, and, ultimately, to death in the most severe cases.[107] Orthostatic (or postural) hypotension is thought to be mediated by α-1 receptor blockade and should be expected from antipsychotics with a high affinity to this receptor, such as ILO, ZIP, RIS, QUE, ASE, HAL, CPZ, and PER,[108] according to animal models. In human beings, CLO, among SGAs, most increases the risk of hypotension, especially at the beginning of treatment, which is the reason behind low initial doses.[94]

Myocarditis and cardiomyopathy

Although not a frequent event, myocarditis risk is highest with CLO, being associated with troponin and C-reactive protein elevation, and eosinophilia.[109] Emerging but sparse case reports also describe cases of myocarditis with QUE.[110,111] In general, regular medical examination as well as blood examination and routine electrocardiography when symptoms arise

(fatigue, palpitations, arrhythmias, shortness of breath upon exertion or at rest, dizziness) can help detect myocarditis and cardiomyopathy early.[112] Early data suggested that successful rechallenge with CLO after myocarditis may be possible in some cases.[113]

According to a large observational study, cardiomyopathy may occur as well with CLO, potentially leading to heart failure.[114] Echocardiography is the gold standard procedure to detect and monitor cardiomyopathy.

Coronary heart disease and stroke

Subjects affected by SMI, including BD and schizophrenia, have consistently been shown to have an up to twofold increased risk of stroke and acute myocardial infarction (AMI), according to several meta-analyses.[115–118] FGAs and SGAs appear to contribute to the increased risk of stroke (OR =1.58, 95% CI 1.01–2.49)[119] and AMI (OR =1.88, 95% CI 1.39–2.54).[120] Comparative data providing information about different SGAs are sparse, and in particular, the cardiovascular safety of newer SGAs, such as ILO, LUR, BRE, and CAR, is missing. In the elderly, higher mortality with FGAs than SGAs seems to be partially explained by a greater risk for stroke and AMI (in addition to ventricular arrhythmias and hip fracture).[121] Broadly, in SMI, HAL, CPZ, OLA, RIS, and QUE have shown the strongest association with cardiovascular events.[69,122–126] The main mechanism through which antipsychotic agents increase CVD rates is through their metabolic effects on weight and glucose and lipid metabolism;[36,37,127] however, some direct toxic action has also been hypothesized based on animal models, in particular involving potassium and calcium channel currents.[128–130]

Pneumonia, acute respiratory failure, and sleep apnea

Two large observational studies suggest that, in patients with schizophrenia, CLO may result in an increased incidence of pneumonia, which persists after CLO is withdrawn and returns when it is reintroduced. This has been associated with sialorrhea.[131–133] There is evidence suggesting that this risk is dose related, in particular with CLO, and is higher in the first weeks of therapy and in elderly patients.[132,134] Polypharmacotherapy may further increase pneumonia risk.[132] While ARI and ZIP do not seem to increase the risk of pneumonia, OLA and RIS increase pneumonia occurrence more than QUE in the elderly population,[135] but no dose-dependent effect has been observed.[132] A meta-analysis including a wider group of patients beyond schizophrenia and BD clearly showed that both FGAs and SGAs increase the risk of pneumonia.[136] More meta-analytic evidence suggested that pneumonia accounts for the higher mortality of FGAs over SGAs.[137] Most importantly, this difference between FGAs and SGAs was confirmed in both elderly and young adult populations.[136] Finally, when prescribing antipsychotics to patients with chronic obstructive pulmonary disease, a frequent comorbidity in BD and schizophrenia,[138,139] respiratory function should be strictly monitored since there is a >1.5-fold increased risk of acute respiratory failure.[140] In case of overdose of AP, respiratory depression can occur as well, due to central sedation and peripheral respiratory muscle impairment.[141]

Sleep apnea moreover has been shown to be more frequent in patients taking SGAs compared with those not on SGAs[138] even after analyses were adjusted for several relevant confounding factors in a large observational study.[142] It could be argued that compounds that increase the risk of weight gain consequently increase the risk of sleep apnea; no specific SGA, however, has shown a worse profile than others.

Pulmonary embolism and venous thromboembolism

Patients with schizophrenia on antipsychotic treatment show a global hypercoagulability state.[143] Pulmonary embolism is a severe adverse event that can occur with antipsychotics, with the concomitant prescription of both FGAs and SGAs increasing the risk from potential substantial harm to a fourfold increased risk, as clearly shown in large observational studies and a meta-analysis.[144,145] Similarly, considering both pulmonary embolism and venous thromboembolism together, some evidence suggests that low-potency FGAs and SGAs have a worse safety profile than high-potency FGAs.[145–147] However, only sparse data are available for individual drugs or specific diagnostic groups.[145] Special attention should be paid in pregnancy and the immediate postpartum, two conditions at increased risk for thrombosis per se.

Gastrointestinal adverse effects

A cross-sectional study of patients with schizophrenia showed that among all antipsychotics, CLO seems to induce the most severe constipation, prolonging colon transit time by up to almost five times, irrespective of gender, age, ethnicity, or length of treatment, undermining treatment adherence.[148] This is likely due to the anticholinergic action[149] and is a dangerous side effect which patients should be monitored for, given the reduced pain sensitivity demonstrated in schizophrenia.[150,151] OLA, CLO, and low-potency FGAs substantially impair colon transit, while drugs with low affinity to cholinergic

receptors, such as BRE, CAR, LUR, and PALI, do not.[152] Conversely, according to a recent meta-analysis on schizophrenia, ARI has been reported to reduce constipation when co-administered with other antipsychotics.[153] D_2 antagonists have been reported to reduce nausea (the early FGAs were widely used for nausea of pregnancy),[153] but the partial D2 agonists, such as CAR, BRE, and ARI, can induce nausea, typically within the first 4 weeks of treatment.[154,155]

Dry mouth, drooling/hypersalivation, and dental caries

Dry mouth is an anticholinergic side effect, most frequent with CLO, OLA, QUE, and low-potency FGAs, that increases the risk of dental caries according to a large population-based study.[156] Sialorrhea is a frequent and paradoxical side effect of CLO.[157] Hypersalivation substantially impairs quality of life and may interfere with social functioning, but has, however, been reported to prevent dental caries.[156] Yet, intense sialorrhea may bear important consequences, such as an increased risk for aspiration pneumonia.[133] ARI has been reported to reduce drooling/hypersalivation, according to a meta-analysis,[153] when antipsychotic polypharmacotherapy is used in schizophrenia.

Hepatotoxicity

The precise pathogenesis of liver damage with the use of antipsychotics is unknown. Several hypotheses have been proposed, but no unique mechanism has been detected since FGAs and SGAs comprise a group of molecules with largely different chemical structures, pharmacokinetics, and pharmacodynamics.[158] Continuous use of antipsychotics is associated with abnormal liver function tests in up to 78% of patients, as shown by an SR.[158] Generally, such alterations consist of elevated transaminases or cholestatic indices, which often occur within the first 6 weeks of treatment, remaining stable or resolving with continuous treatment.[158] Although asymptomatic liver enzyme abnormalities may be common, significant liver enzyme elevations are rare, but can occur with OLA, QUE, and RIS.[159] CPZ has been most frequently associated with acute liver injury, even resulting in fatal hepatic failure, but such events are rare with other antipsychotics.[158] Sparse comparative data are available, but CLO seems to confer a relatively high risk of liver damage, in particular compared with HAL.[160] SGAs have been associated with chronic liver disease in patients with BD in a large observational study.[161] During the first 3 years of antipsychotic treatment in patients with the first-episode schizophrenia, nonalcoholic fatty liver disease was associated with the presence of the major components of metabolic syndrome in an RCT.[162] Liver function should be monitored in patients administered SGAs.[163] Predisposing factors to liver damage include not only older age, high daily dosage/serum concentrations, alcohol abuse, and a history of hepatic disease[160] but also some of the evidence-based combination treatments for BD, such as valproate.[164] PALI, which does not undergo first-pass hepatic metabolism, and ZIP, which is only partially metabolized by cytochrome P450 enzymes, are safest for the liver.

Urinary and kidney function

PALI, CLO, ILO, OLA, QUE, and RIS are excreted in urine, while ARI and ZIP are excreted in feces so that these two drugs do not require dose adjustment in patients with renal impairment, at least regarding their oral formulations.[39] Conversely, LUR requires dose adjustment when renal failure is present, and CAR and AMI, which are solely excreted by the kidneys, should be avoided in case of renal failure.[165] Moreover, since electrolyte disturbances can occur when renal function is impaired, AMI and SER should be used with caution and with accompanying electrolyte monitoring due to potential cardiac toxicity. Drugs with strong anticholinergic properties, such as CLO, OLA, and low-potency FGAs, can induce acute urinary retention, but urinary acute retention can also occur with ZIP or RIS, via central dopaminergic and serotoninergic mechanisms as described in an SR.[166] SGAs should be used with caution in particular in the elderly due to their role in increasing the risk for hospitalization for acute kidney injury[167] and hypotension with risk of falls, as documented by a cohort study involving older adults. On the other hand, antipsychotics with strong sedative effects can cause urinary incontinence, as can be the case with CLO, especially when associated with antipsychotic polypharmacotherapy.[168,169] Although evidence on the topic is substantially lacking, nevertheless, the known adverse effects on kidney function after very long-term lithium treatment give rise to the recommendation that special caution be paid in patients on lithium combined with PALI, CLO, ILO, OLA, QUE, and RIS, a common drug regimen in evidence-based guidelines for BD.[164,170] Finally, acute renal failure can occur in the context of rhabdomyolysis as a severe consequence of malignant neuroleptic syndrome, as described later.

Leucocytopenia, agranulocytosis, and thrombocytopenia

Neutropenia, thrombocytopenia, and agranulocytosis can typically occur not only with CLO and phenothiazine but

also with other antipsychotics such as RIS and QUE, in particular when the patient is on polypharmacotherapy with mood stabilizers.[39,112] Case reports suggest that in patients with leukopenia (but not agranulocytosis), rechallenge with CLO is more often successful than not (70%), especially under co-treatment with low-dose lithium.[113]

Osteopenia, osteoporosis, and fractures

Bone mineral density in patients with schizophrenia treated with antipsychotics is negatively related with age and positively with duration of antipsychotic treatment and illness duration,[171] ultimately increasing the risk of osteoporosis.[172–174] While preliminary data suggest an influence of elevated prolactin levels on bone turnover markers in schizophrenia treated with antipsychotics,[175] suggesting that prolactin-raising drugs should reduce bone mineral density,[171] more studies are needed to better determine the precise mechanisms underlying the effect of antipsychotics on bone metabolism, as per an SR.[176] Alongside with CVD, fractures explained part of the higher mortality with FGAs compared with SGAs in the elderly.[121] However, fractures have been reported with all antipsychotics in patients with schizophrenia[177] according to an SR. Osteopenia, osteoporosis, and fractures should be of particular concern in females during perimenopause when the risk for osteoporosis is elevated.

Falls

Considering that patients treated with antipsychotics have an increased risk for impaired bone metabolism for a number of reasons, including reduced physical activity and reduced sun exposure, falls due to side effects of AP can result in an increased risk of fractures, in particular within the first 30 days of treatment.[178] However, in elderly patients, antipsychotics seem to be associated with a lower risk of falls than either antidepressants[179] or benzodiazepines in the first 24 hours after the first administration.[180] It remains difficult to establish whether the risk for falls with AP is due to sedation, visual impairment, hypotension, or motor side effects, but most likely a multi-factorial model can best explain the increased risk. Data are lacking about the incidence of falls in adults with schizophrenia and BD, although it is known that this group is at an increased risk of fall-related fractures.[177]

Binge eating, pathological gambling, and impulse control disorders

Binge eating is linked to receptor affinity to histaminergic receptors and is frequently observed with the prescription of OLA and CLO according to an RCT.[181] Because of its partial agonist effect on dopamine receptors, ARI may increase the risk of impulse control disorder, hypersexuality, compulsive shopping, and pathological gambling according to preliminary case report data and one epidemiological study.[182–184] Nevertheless, ARI usually has a net effect of dopamine antagonism, shown by worsening instead of improvement in motor symptoms in patients with Parkinson's disease.[185] Hence, until more conclusive data exist and although the case reports may be related to symptoms of the disorders for which ARI was prescribed (as also indicated in the US Food and Drug Administration label of ARI), the risk for pathological gambling should be assessed when prescribing ARI to impulsive young patients with a history of substance abuse and to those with a high novelty-seeking profile.[186]

Tobacco use

Smoking is frequently a comorbidity in SMI,[143] but antipsychotic treatment does not seem to increase the risk of smoking. Actually, both typical antipsychotics and CLO have been shown to increase the odds of smoking cessation in patients with schizophrenia.[187,188] However, tobacco smoke increases the metabolism of several psychotropic medications through inducing enzymes in the cytochrome P450 system, CYP1A2 in particular. Thus, the pharmacokinetics of OLA, and CLO are influenced in clinically relevant ways by smoking habits, in that smoking can decrease circulating drug levels, with a required increase of drug dose by up to 50%[189] and risk of overdose upon smoking cessation. The cognitive-enhancing properties of pulsatile nicotine delivery may constitute self-treatment by patients with SMI in an attempt to improve cognitive function, impaired due to both the disease and its treatment.[190]

Sexual and reproductive system dysfunction

Sexual dysfunction is frequent during antipsychotic treatment and can be due to several factors, including co-treatment with two dopamine D2 antagonists,[191] long duration of illness, and TD in schizophrenia.[192] Hyperprolactinemia can cause sexual and reproductive system dysfunction, including decreased libido, erectile dysfunction, and anorgasmia, as well as reproductive system dysfunction, such as gynecomastia, galactorrhea, and oligo- or amenorrhea in women. All antipsychotics raise prolactin levels. AMI, RIS, and PALI do it the most.[193–195] Conversely, drugs with a high α-adrenergic antagonism can induce priapism[196,197] and retrograde ejaculation, which may be disturbing for patients prone to delusions.[198,199] It should also be considered that drugs with a high sedative profile may indirectly diminish sexual arousal and desire.[199] Restricted comparative data

limit conclusions about the relative ease with which different compounds affect sexual function.

Endocrine diseases (diabetes ketoacidosis, hypothyroidism, and hyponatremia)

Although no relevant clinical studies are available, diabetic ketoacidosis is frequently reported in case reports of patients taking antipsychotics, in particular OLA, CLO, and RIS.[200,201]

Hypothyroidism can occur with QUE, ARI, RIS, or OLA, in patients treated for BD in a large cohort. However, the frequency of hypothyroidism with SGAs is lower than with lithium.[202] While there are case reports of QUE being associated with thyroid dysfunction,[203] no clinically relevant risk of thyroid disturbance has been described in association with antipsychotics.

Hyponatremia risk appears to be increased with antipsychotic treatment and may be underestimated when several hyponatremia-inducing drugs are prescribed together, as reported in a large observational study.[204] However, no solid literature provides comparative data for different compounds, and no sodium monitoring is recommended when antipsychotics are started. In addition, hyponatremia may be related to polydipsia, a clinical feature often associated with schizophrenia.[205]

Hyperprolactinemia and prolactinoma

The degree of hyperprolactinemia depends on the D_2 receptor occupancy[206] and on the antagonist properties of the antipsychotics.[207] Thus, antipsychotics with a strong D_2 affinity and antagonist pharmacodynamic properties increase prolactin serum levels the most, namely, AMI, HAL, PALI, and RIS.[28,208] Moderate hyperprolactinemia has been described with SER, LUR, and ZIP; mild hyperprolactinemia has been described with ILO, CPZ, OLA, and ASE; and no hyperprolactinemia has been seen with the use of QUE and CLO.[28,209] On the contrary, partial D2 agonists, such as ARI, BRE, and CAR, can lower prolactin levels, even below drug-free baseline, and adjunctive ARI has been shown to decrease hyperprolactinemia associated with other antipsychotics.[28,209–211] Several cases have been reported describing antipsychotic use and prolactinoma,[212] in particular in cases using AMI[213,214] or RIS.[215–217] However, no solid data are available, and thus, no conclusions can be drawn on the association of antipsychotics and prolactinoma.[218]

Breast and cervical cancers

Patients with SMI have lifestyle-related risk factors for cancer (smoking, caffeine intake, alcohol, lack of exercise) and often undergo less medical screening (for breast and cervical cancers for instance) than the general population.[219,220] These factors could at least partially explain the higher cancer mortality rates,[221] in particular for respiratory tumors,[222] in patients with SMI, despite some evidence that suggests lower overall cancer rates.[223] One mechanism that could contribute to an increased risk of tumorigenesis is antipsychotic-related hyperprolactinemia (for breast and prostate cancers). However, in two recent reviews, no causal linkage has been demonstrated between cervical and breast cancers and antipsychotics.[224,225] Moreover, comparative data from a large, national representative dataset have shown that RIS does not confer a higher risk of breast cancer compared to other antipsychotics, either FGAs or SGAs, while controlling to some degree for illness and behavior-related risk factors in individuals receiving antipsychotics.[226] Thus, no conclusive evidence supports an increased risk of cancer in relation to the use of antipsychotics in schizophrenia or BD.[227]

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is characterized by hyperthermia, rigidity, elevated creatinine phosphokinase (CPK) more than four times of the upper limit (and up to myoglobinuria), changes in mental status, and autonomic dysregulation.[204,228]

While the exact incidence of NMS is unclear,[229] it has potentially life-threatening consequences. NMS can occur with both FGAs and SGAs, in particular with the typical antipsychotics flupentixol, HAL, fluphenazine, thioridazine, CPZ, trifluoperazine, LOX, periciazine, methotrimeprazine, prochlorperazine, and zuclopenthixol, as well as with CLO, OLA, RIS, QUE, ARI, PALI, ASE, and ZIP.[230] While no clear consensus exists,[230] SGA-associated NMS seems to be of lower frequency, severity, duration, and lethality than NMS associated with FGAs.[231,232] CLO may have the highest risk of NMS among SGAs,[230] although patient-related factors may also play a role. Beyond specific pharmacologic compounds, several environmental factors can increase the risk of NMS, including the use of high doses, parenteral administration, polypharmacotherapy, physical restraint, dehydration, high temperature, older age and multiple medical comorbidities, previous history of NMS, family history of catatonia, and muscle channelopathy.[230]

Mortality

Several studies report that higher antipsychotic dosage and polypharmacy increase the risk of mortality in patients with schizophrenia,[233] with a higher risk for FGAs compared to SGAs.[121] Death is mediated by pneumonia, CVD, hip fracture, and cardiac arrhythmias, among other dysfunctions.[121,137]

Withdrawal and rebound syndromes

Withdrawal and rebound syndromes related to antipsychotic treatment depend on the pharmacokinetic and pharmacodynamic profiles of the discontinued pre-switch antipsychotics and of the post-switch antipsychotics if withdrawal symptoms occur during antipsychotic switching. While the pharmacokinetic profile influences the timing of the occurrence of such syndromes, pharmacodynamics determines their symptomatic presentation.[35] Withdrawal or rebound syndromes are central and peripheral phenomena induced by the sudden reversal of receptor blockade when the pre-switch medication is discontinued too quickly and the post-switch drug is a comparatively less efficient receptor antagonist.

One of the factors associated with withdrawal reactions is plasma half-life. Generally, it takes approximately five times a compound's half-life for it to be completely eliminated from plasma; such pharmacokinetic parameters should be taken into account when stopping a treatment or switching to a different antipsychotic. The antipsychotics with the shortest half-life are QUE immediate release and ZIP (<12 hours). ILO, AMI, CLO, HAL, and PER have a relatively short half-life (12–24 hours), while RIS/PALI and OLA have a moderately short one (20–36 hours). ARI, BRE, CAR, and SER have the longest half-lives (50–100 hours). The most important determinant of rebound is how long the drug attaches to the receptor; CLO for instance spends very little time at the receptor; OLA and QUE are the next shortest. Conversely, HAL attaches for a very long time.[234]

From a clinical perspective, upon withdrawal from a drug, one should expect peripheral manifestations opposite to those that were initially blocked by the drug. For example, one would expect diarrhea, sweating, nausea, vomiting, and hypotension when a medication with a strong anticholinergic activity is abruptly withdrawn or tachycardia and hypertension when an agent with potent alpha1 blocking potential is rapidly stopped. The rebound syndrome is caused by the exposure of a previously blocked and thus upregulated receptor system to its natural ligand.[35] Typically, histaminergic rebound includes anxiety, agitation, insomnia, restlessness, and EPS; cholinergic rebound is marked by agitation, confusion, and EPS; and dopaminergic rebound can manifest as increased psychotic symptoms, mania, agitation, aggression, akathisia, or dyskinesia.[35] Hence, particular attention should be paid when switching from antipsychotics with strong antihistaminergic, anticholinergic, and/or antidopaminergic properties to those with lower affinities for these receptors. In addition to such "pharmacodynamic rebound" syndromes, "pharmacokinetic rebound" can occur when the post-switch antipsychotic is inadequately dosed or has a much longer half-life than the pre-switch antipsychotic. In this scenario, unless cross-titration is used, and depending on the relative half-lives of the discontinued and the new drug, the patient can suffer from temporary underdosing or overdosing.[35,235]

Pregnancy and breastfeeding

During pregnancy, OLA, CLO, and QUE, alongside with other antipsychotics, may be expected to increase the risk of gestational diabetes, hypertension, thromboembolism, or congenital malformations. However, evidence on the safety of these agents during pregnancy remains limited and conflicting. While an SR suggested the use of FGAs instead of SGAs during pregnancy, due to the fact that these latter agents may increase the risk of gestational diabetes and large-for-gestational-age babies,[236] more recent large-scale observational studies do not confirm such a concern in terms of mother and newborn safety; these studies did, on the other hand, verify an increased risk for perinatal complications and low birth weight with FGAs.[237,238] A recent expert panel recommended the use of OLA during pregnancy due to the large amount of safety data;[239] the same panel suggested that QUE and RIS were also safe for use during pregnancy.[239] However, a recent large database study found that RIS use was associated with a small risk of cardiac and overall malformations even after adjustment to potential confounders.[240]

During breastfeeding, QUE, OLA, and ARI can be used; the relative infant doses (RIDs) for these agents are low (<2%).[239] RIS may be used under medical supervision, while AMI and CLO should be avoided.[195] Safety in lactation depends on the properties of the drug that determine its ease of passage into breast milk.

Sleepwalking and other sleep disturbances

Several case reports have described sleepwalking or other sleep disturbances (such as daytime sedation and sleep apnea described earlier) in association with antipsychotics administration; however, it remains debatable whether antipsychotics contribute to the risk of sleep disturbances or may, in fact, help to reverse them.[241] Overall, no definitive evidence is available on this matter.

Hypothermia

Increasingly, sporadic cases of hypothermia have been described when antipsychotics were administered; while a precise mechanism, namely, 5HT2 antagonism, has been

suggested, large studies with consistent (comparative) data are still lacking.[242]

Discussion

When assessing a medication, both efficacy and tolerability are equally important, not only because adverse effects can reduce subjective well-being and adherence but also because adverse effects can adversely affect treatment outcomes.[50,243] Notwithstanding the fact that differences in efficacy among antipsychotics are relatively small and difficult to predict (with the one exception of CLO, which has shown a clear advantage over other agents for treatment-resistant schizophrenia), the ability to accurately predict differences in treatment-emergent adverse effects is critical. Such effects depend, at least in part, on distinct pharmacodynamic profiles of the various drugs.[28,39,244] Although the differentiation of antipsychotics into FGAs and SGAs is based on history and is overly simplistic, obscuring the different profiles of individual antipsychotics within each class that markedly diverge in their safety and tolerability profiles, this classification is still used and has some heuristic value. According to our review, generally, FGA-related adverse effects that affect symptomatic and functional outcomes include neuromotor disorders as well as the possibility of worsening negative symptoms, social withdrawal, and cognitive dysfunction. These effects may explain the lower adherence to FGAs compared to SGAs. However, the use of SGAs often leads to serious adverse cardiometabolic effects, individual agents carrying a different propensity for weight gain and metabolic side effects. Importantly, the use of SGAs appears to be associated with less cognitive impairment than that of FGAs. With respect to management, treatment-emergent effects related to the use of FGAs, such as TD, are challenging to treat but the more common EPS respond well to anticholinergic medication. Sometimes, however, this is at the expense of worsening cognitive function. SGA-induced "metabolic" comorbidity can theoretically be prevented or reduced through the adoption of a multidisciplinary approach of active monitoring plus careful attention to diet and activity level. However, diet alone does not prevent SGA-induced weight gain; although weight loss has been demonstrated,[245,246] no evidence of a positive dietary modulation of SGA-induced metabolic effects has thus far been evidenced.[247] A meta-analysis of physical exercise-based intervention for both BD and schizophrenia showed an increase in the physical activity of patients but no clear beneficial effects on physical parameters.[248] A meta-analysis on mixed dietary and physical exercise interventions found very small positive effects (eg, a BMI reduction of 1 point). It is possible, however, that high heterogeneity and a relatively low quality of trials may have biased the results.[249] Nevertheless, methodologically the best and largest individual RCT on this topic showed no real benefit of behavioral interventions on overall metabolic parameters.[250]

Important to keep in mind for the treatment of schizophrenia is that although FGAs and SGAs are equally effective in treating positive symptoms, negative and cognitive symptoms may be aggravated by FGAs.[55,251] In the past, outcome measures were predominantly based on symptom reduction, but today, improvements in quality of life and overall functional "recovery" constitute "real-world" therapeutic aims. Subjective measures are what matters most for current gold standards of outcome, and both negative and cognitive symptoms are more relevant here than the presence or absence of positive psychotic symptoms. For BD, the depressive polarity is most common[252] and is also associated with a worse global outcome and with more functional impairment than is the presence of manic episodes.[253] The evidence for antipsychotic efficacy in the treatment of depression in BD is sparse, except for positive reports on QUE, LUR, OLA, and CAR.[254] There is strong evidence, however, for most SGAs of efficacy in the treatment of mania and manic-predominant polarity patients.[255,256] The clinical challenge in the management of mania remains, nonetheless, because of poor treatment adherence and symptom control rooted in poor insight and comorbid substance abuse.[257,258]

Relying on the 50 years old yet still currently applicable theoretical framework of "behavioral toxicity",[47,48] we conclude that SGAs have broadened the range of therapeutic options in the treatment of schizophrenia and BD, rapidly gaining first-line rank, especially in international clinical guidelines for the evidence-based, long-term treatment of both schizophrenia and BD.[170,259–261] The broad division of antipsychotics into FGAs and SGAs, although flawed, allows for individualized treatment choices that balance clinical and tolerability concerns. These choices, to date, are mostly limited to careful clinical observation and assessment. Although modern, neurobiologically based instruments – such as pharmacogenetic tests or biomarker-based decision making – have been developed, they are only, as yet, partially implemented. They currently show guarded promise for optimal selection of individually tailored antipsychotic agents.[262,263]

The limitation of this review is a dearth of information on newer compounds, such as BRE, LUR, and CAR.

Furthermore, information about long-term effects is limited since most trials are of short duration. Data on the incidence of potentially serious adverse effects (NMS, agranulocytosis, diabetic ketoacidosis, pathological gambling, and pancreatitis) and on long-term side effects (eg, type 2 diabetes, TD, stroke, AMI, cancer, osteoporosis) remain inconclusive. Long-term effects on fetuses exposed in utero to these drugs remain unknown.

Using a framework that balances efficacy against target symptoms with the potential for behavioral toxicity, this review brings together what is currently known about the clinical use of antipsychotics. Methodologically improved clinical trials and large, prospective, longitudinal population-based observational studies will, in the future, fill the gaps described earlier and provide further evidence on the safety and tolerability of antipsychotic medications.

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