CNS Drugs (2013) 27:545–572
DOI 10.1007/s40263-013-0079-5

REVIEW ARTICLE

Withdrawal Symptoms and Rebound Syndromes Associated with Switching and Discontinuing Atypical Antipsychotics: Theoretical Background and Practical Recommendations

Anja Cerovecki · Richard Musil · Ansgar Klimke · Florian Seemüller · Ekkehard Haen · Rebecca Schennach · Kai-Uwe Kühn · Hans-Peter Volz · Michael Riedel

Published online: 3 July 2013

Abstract With the widespread use of atypical or second-generation antipsychotics, switching treatment has become current practice and more complicated, as the pharmacological profiles of these agents differ substantially despite their similarity in being 'atypical'. All share the ability to block dopamine D_2 receptors, and most of them also block serotonin 5-HT_{2A} receptors. Apart from these common features, some atypical antipsychotics are also able to block or stimulate other dopamine or serotonin receptors, as well as histaminergic, muscarinergic or adrenergic receptors. As a result of the varying receptor affinities, in switching or discontinuing compounds several possible pitfalls have to be considered, including the occurrence of withdrawal and rebound syndromes. This article reviews the pharmacological background of functional blockade or stimulation of receptors of interest in regard to atypical antipsychotics and the implicated potential withdrawal and rebound phenomena. A MEDLINE search was carried out to identify information on withdrawal or rebound syndromes occurring after discontinuation of atypical antipsychotics. Using the resulting literature, we first discuss the theoretical background to the functional consequences of atypical antipsychotic-induced blockade or stimulation of neurotransmitter receptors and, secondly, we highlight the clinical consequences of this. We then review the available clinical literature on switching between atypical antipsychotics, with respect to the occurrence of withdrawal or rebound symptoms. Finally, we offer practical recommendations based on the reviewed findings. The systematic evaluation of withdrawal or rebound phenomena using randomized controlled trials is still understudied. Knowledge of pharmacological receptor-binding profiles may help clinicians in choosing adequate switching or discontinuation strategies for each agent. Results from large switching trials indicate that switching atypical antipsychotics can be performed in a safe manner. Treatment-emergent adverse events during or after switching are not always considered to be, at least in part, associated with

Electronic supplementary material The online version of this article (doi:10.1007/s40263-013-0079-5) contains supplementary material, which is available to authorized users.

A. Cerovecki · R. Musil (✉) · F. Seemüller · R. Schennach · M. Riedel
Department of Psychiatry and Psychotherapy, Ludwig Maximilian University, Nussbaumstr. 7, 80336 Munich, Germany
e-mail: Richard.musil@med.uni-muenchen.de

A. Klimke
Clinic for Psychiatry and Psychotherapy, Vitos Waldkrankenhaus Köppern, Emil-Sioli-Weg 1-3, 61381 Friedrichsdorf, Germany

E. Haen
Clinical Pharmacology, Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany

K.-U. Kühn
Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany

H.-P. Volz
Clinic for Psychiatry and Psychotherapy, Schloss Werneck, Werneck, Germany

M. Riedel
Vinzenz von Paul Hospital, Rottweil, Germany

the pre-switch antipsychotic. Further studies are needed to substantiate the evidence gained so far on different switching strategies. The use of concomitant medication, e.g., benzodiazepines or anticholinergic drugs, may help to minimize symptoms arising from the discontinuation or switching of antipsychotic treatment.

1 Introduction

With the introduction of new compounds, a multitude of atypical antipsychotics have become available for the treatment of schizophrenic disorders. This situation has led to more frequent switching of medication in the case of adverse events (AEs) or ineffective treatment. Although all second-generation antipsychotics are called 'atypical', they form a heterogeneous group of substances differing substantially in their receptor-binding profiles and resulting clinical consequences (see Table 1).

The likelihood of receptor-mediated effects occurring can be anticipated to a certain extent on the basis of these receptor-binding profiles, taking expected occupancy of these receptors under therapeutic conditions into account. The main receptor-mediated effects of atypical antipsychotics occur via dopaminergic, serotonergic, histaminergic, cholinergic and adrenergic pathways. It has been proposed that symptoms associated with the discontinuation of psychotropic drugs be separated into three different types [1]: (1) withdrawal symptoms (minor and major new symptoms [2]) (2) rebound syndromes and (3) supersensitivity syndromes [1, 3–5]. Withdrawal symptoms are characterized by the appearance of somatic symptoms after discontinuation of psychotropic drugs such as withdrawal-induced hyperthermia after discontinuation of clozapine [6]. Rebound phenomena comprise serotonergic, histaminergic and cholinergic rebound [7–11]. Supersensitivity syndromes subsume tardive dyskinesias (TD) and supersensitivity psychosis, sometimes also called "rapid-onset psychosis" [12]. In Sect. 2 of this article, we discuss the theoretical background to the functional consequences of atypical antipsychotic-induced blockade or stimulation of various receptors. The clinical consequences of this are highlighted in Sect. 3. Furthermore, a brief overview in table form of the different receptor subtypes, their distribution in the CNS and of symptoms resulting after receptor blockade or upon stimulation are presented in Tables 2, 3, 4, 5 and 6. In Sect. 4, literature is reviewed for relevant symptoms associated with switching or discontinuation of the various atypical antipsychotics and practical recommendations are given when considering switching to a certain compound. In many cases treatment-emergent AEs (TEAEs) are interpreted as being related to the newly prescribed medication, leading to unnecessary discontinuation of the new compound. In this regard, knowledge of withdrawal syndromes is crucial for planning adequate switching strategies. In the last part of this review, we summarize important aspects of switching or discontinuation of atypical antipsychotics.

2 Theoretical Background

2.1 Dopamine

Pharmacological and genetic analyses differentiate between dopamine D_1 (D_1- and D_5) and D_2 (D_2-, D_3- and D_4) type receptors [13–15]. All efficacious and approved antipsychotics block D_2 receptors, however to a different extent (see Table 1).

There are four different dopaminergic pathways in the CNS [16, 17]. Distribution of $D_{1–4}$ receptors in the brain, functional effects upon blockade or stimulation and their relevance to schizophrenia are shown in Table 2.

To comprehend rebound and withdrawal phenomena relating to dopaminergic receptor functions it is important to understand the pathophysiology of motor AEs resulting from a blockade of these receptors (see Table 2). Early dyskinesia probably derives from an overshooting, contraregulatory dopamine release, whereas parkinsonism is a consequence of a striatal dopamine reduction. The pharmacological mechanism of akathisia is still unclear. Late dyskinesia is attributed to a hypersensitivity of striatal postsynaptic dopamine receptors [18, 19]. The exact pathophysiological mechanism of neuroleptic malignant syndrome is likewise unknown, although it has been suggested that this phenomenon might be due to an almost complete blockade of D_2 receptors [20].

It has been further hypothesized that in schizophrenia D_2 receptors are generally in a high affinity state, making schizophrenic patients supersensitive to dopamine [21].

Apart from pharmacological effects that are attributed to certain receptor subtype functions, there are numerous interactions of receptor subtypes both within a class of receptors, e.g. D_1 receptors interacting with D_2 receptors, and between different classes of receptors, e.g. D_2 receptor function interacting with serotonin 5-HT_{2A} function (see Table 7).

Some of these receptor interactions (see Table 7) have been proposed to form the basis of the 'atypical' properties of atypical antipsychotics, leading to a lower propensity than typical antipsychotics to cause extrapyramidal motor symptoms (EPMS) and TD and having at least some effects on negative and cognitive symptoms [22].

2.2 Serotonin

There are several subtypes of serotonergic receptors (5-HT_1–5-HT_7) [23, 24]. Expression profiles of the most

Table 1 Binding affinities measured as Ki values (nM/l) [in some cases (*) Kd values in nM] of atypical antipsychotics and haloperidol at selected receptors. The smaller the number, the greater the receptor affinity and thus expected mediated effect [110, 196–216]

Receptor	Amisulpride	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Sertindole	Ziprasidone	Haloperidol
D_1	>10000 [196]	265 [197]	1.4 [198]	85 [199]	216 [200]	No data	31 [199]	510 [201]	455 [199]	75 [199]	12 [202]	9.5 [202]	25 [199]
D_2	3 [196]	0.34[§] [197]	1.3 [198]	125 [199]	21.4 (D_2L) [110]	1.68 [203]	11 [199]	4.8 [204]	160 [199]	3 [199]	0.45 [202]	2.8 [202]	1 [199]
D_3	3.5 [196]	0.8 [197]	0.42 [198]	219 [198]	7.1 [200]	No data	35 [198]	6.9 [204]	389 [198]	6.9 [198]	2.6 [205]	7.2 [206]	2.8 [198]
D_4	2369 [196]	44 [197]	1.1 [198]	21 [199]	25 [200]	No data	27 [199]	30 [204]	1412 [198]	7 [199]	11 [205]	32 [206]	5 [199]
5-HT_{1A}	>10000 [196]	1.7[§] [197]	2.5 [198]	770[§] [199]	93.1 [110]	6.75[§] [203]	>1000 [199]	590 [204]	2450[§] [199]	490 [199]	2600[#] [215]	3.4[§] [206]	7930[#] [215]
5-HT_{2A}	8304 [196]	3.4[§] [197]	0.07 [198]	12 [199]	5.6 [200]	2.03 [203]	4 [199]	1.0 [204]	220 [199]	0.6 [199]	0.2 [202]	0.4 [206]	78 [199]
5-HT_{2C}	>10000 [196]	15[§] [197]	0.035 [198]	8[#] [216]	42.8 [207]	415 [208]	11[#] [216]	48* [209]	615 [199]	26[#] [216]	1.2[#] [216]	1.3[#] [216]	3085 [199]
5-HT_6	4154 [196]	229 [198]	0.25 [198]	8.9 [198]	63.1 [110]	No data	3.2 [198]	No data	2290 [198]	2187 [198]	0.7 [210]	166 [198]	3630 [198]
5-HT_7	11.5 [196]	35 [198]	0.11 [198]	6.5 [198]	112 [110]	0.459 [203]	37 [198]	10 [211]	56 [198]	0.7 [198]	11 [210]	2.5 [198]	89 [198]
α_1	>10000 [196]	324 [198]	1.2 [198]	7 [199]	4.4 [212]	47.9 [203]	19 [199]	10.1* [209]	7 [199]	2 [199]	1.4 [205]	10 [206]	46 [199]
α_2	1114 [198]	69 [198]	1.2 [198]	29 [198]	162 [110]	40.7 [203]	148 [198]	80* [209]	562 [198]	8.1 [198]	640 [213]	257 [198]	871 [198]
α_{2B}	No data	191 [198]	0.32 [198]	28 [198]	162 [110]	No data	331 [198]	No data	83 [198]	9.5 [198]	450 [213]	240 [198]	562 [198]
α_{2C}	1540 [196]	12 [198]	1.2 [198]	1.6 [198]	16.2 [110]	10.8 [203]	41 [198]	No data	38 [198]	1.8 [198]	450 [213]	42 [198]	132 [198]
H_1	>10000 [196]	61 [197]	1.0 [198]	6 [199]	437 [212]	>1000 [203]	7 [199]	32 [204]	11 [199]	155 [199]	440 [202]	47 [206]	3630 [199]
H_2	>10000 [196]	7079 [198]	6.2 [198]	1230 [198]	No data	No data	3162 [198]	No data	6606 [198]	479 [198]	No data	>10000 [198]	3162 [198]
M_1	>10000 [196]	3890 [198]	8218 [198]	1.9[§] [199]	4898 [110]	>1000 [203]	1.9 [199]	8800* [209]	120 [199]	>5000 [202]	260 [202]	>10000 [202]	1475 [199]

[§] Indicates partial agonistic properties; [#] indicates inverse agonistic properties; * indicates Kd value

Table 2 Distribution of dopamine receptor subtypes and functional effects of blockade or stimulation and their clinical relevance to schizophrenia, bipolar disorder and major depressive disorder

Receptor subtype	Expression	Functional effect if blocked	Functional effect if stimulated	Clinical relevance to schizophrenia, bipolar disorder, major depression	Relevance of these receptors to antipsychotic treatment[a]
D_1 (D_1 subtype) (exclusively postsynaptic)	Prefrontal cortex, nigrostriatal, mesolimbic, mesocortical areas and lower levels in the hippocampus, cerebellum, thalamus, hypothalamus [13]	Functional disinhibition of dopaminergic neurons resulting in increased dopamine release	Inverted-U dose response of cognitive impairment [217, 218], stimulatory effect on locomotor activity, reward and reinforcement [13]	Reduction in EPMS via counteraction of D_2 blockade in nigrostriatal pathway, improvement of energy and modulation of working memory [219]	Asenapine, ziprasidone, to a lesser extent clozapine, olanzapine, risperidone, sertindole, haloperidol
D_2 (D_2 subtype) (pre- and postsynaptic)	Mesolimbic	Reduction in positive symptoms	Reward and reinforcement [13]	Antipsychotic effect	All first- and second-generation antipsychotics, strongest affinity for aripiprazole and weakest for clozapine and quetiapine; local selectivity
	Mesocortical	Secondary negative symptoms	Memory dysfunctions [220]	Cognitive dysfunction, anhedonia, reduced motivation	
	Nigrostriatal	Postsynaptic: EPMS	Presynaptic: decrease in locomotor activity [13]	Early and late dyskinesia, parkinsonism, akathisia, malignant neuroleptic syndrome [221]	
	Tuberoinfundibular	Prolactin increase	Inhibition of prolactin release	Gynaecomastia, galactorrhoea, amenorrhoea, decreased bone density	
D_3 (D_2 subtype) (pre- and postsynaptic)	Limbic areas, tuberoinfundibular, lower levels in other areas [13]	Prolactin increase	Moderate inhibitory action on locomotion [222], reward and reinforcement [13], modulatory effects on D_2 functions [13, 223]	Gynaecomastia, galactorrhoea, amenorrhoea, decreased bone density	Amisulpride, aripiprazole, asenapine, iloperidone, paliperidone, risperidone, sertindole, ziprasidone, haloperidol, to a lesser extent olanzapine
D_4 (D_2 subtype) (pre- and postsynaptic)	Frontal cortex, nigrostriatal, limbic areas, thalamus [224], hippocampus [225]	Reduced locomotion and behavioural response to novelty [224], attenuates cognitive deficits [226]	Hyperlocomotion, reward effects	Possible contribution to antipsychotic effects, improving symptoms in combination with D_2 blockade [226, 227]	Asenapine, haloperidol, risperidone, to a lesser extent aripiprazole, clozapine, iloperidone, olanzapine, sertindole, ziprasidone

[a] Relationship was assumed if binding affinity measured by Ki value was ≤10 nM/l and defined as being to a lesser extent if Ki values were ≤100 nM/l

EPMS extrapyramidal motor symptoms

Table 3 Distribution of serotonin receptor subtypes and functional effects of blockade or stimulation and their clinical relevance to schizophrenia, bipolar disorder and major depressive disorder

Receptor subtype	Expression	Functional effect if blocked	Functional effect if stimulated	Clinical relevance to schizophrenia, bipolar disorder, major depression	Relevance of these receptors to antipsychotic treatment[a]
5-HT_{1A} (pre- and post-synaptic)	Raphe nuclei, limbic areas (e.g., hippocampus, amygdala, lateral septum) [228–230], lower levels in cerebral cortex, thalamus, hypothalamus, basal ganglia [228, 229]	Improvement of cognitive impairments in schizophrenia (postsynaptic) [231–233]	Regulation of circadian rhythm, body temperature, nociception, food intake, sexual behaviour, improving cognitive deficits (presynaptic) [26], anxiolytic and antidepressive activity (presynaptic) [234], amelioration of EPMS (postsynaptic) [235–237]	Anxiolytic/antidepressive effect, improvement of cognitive deficits [26, 27], improvement of EPMS [235–241]	Aripiprazole, lurasidone, ziprasidone (partial agonists), asenapine, to a lesser extent iloperidone
5-HT_{2A}	Prefrontal cortex, claustrum, basal ganglia [242], hippocampus	Sedation, lengthening of delta sleep phase, decrease in blood pressure, questionable improvement of negative symptoms, attenuation of EPMS [243–246]	Activation of GABAergic neurons, inhibition of the release of acetylcholine and glutamate; resulting in sensory overload	Reduction of REM sleep, modulation of limbic functions, appetite and food intake, pain and sleep, improvement of EPMS [243–246]	Aripiprazole (partial agonist); asenapine, iloperidone, lurasidone, paliperidone, olanzapine, risperidone, sertindole, ziprasidone, to a lesser extent clozapine, haloperidol
5-HT_{2C}	Plexus choroideus, cortex, hippocampus, striatum [242], substantia nigra	Increase in appetite, weight gain, enhancement of dopamine release in cortex and nucleus accumbens, with possible positive effects on cognitive function, positive and negative symptoms and depression [247], amelioration of EPMS [248] and hyperprolactinemia	Suppression of dopamine release in cortex and nucleus accumbens [247]	Metabolic syndrome, weight gain, modulation of cognitive, positive, negative and depressive symptoms [26, 247], improvement of EPMS [248]	Asenapine, clozapine, sertindole, ziprasidone, to a lesser extent aripiprazole (partial agonist), iloperidone, olanzapine, paliperidone, risperidone
5-HT_6	Striatum, olfactory tubercles, limbic areas (hippocampus, nucleus accumbens) [242]	Attenuation of cognitive deficits [26, 27, 249], possibly positive effects on psychotic symptoms [26]	Antidepressant potential, cognitive enhancement, anti-obesity effects [249, 250]	Improvement of cognitive deficits [26, 27], antipsychotic properties	Asenapine, clozapine, olanzapine, sertindole, to a lesser extent iloperidone
5-HT_7	Low levels in striatum [242]	Attenuation of cognitive deficits [26, 27], possibly positive effects on psychotic symptoms [26], anxiolytic and antidepressive effects [251]	No data found	Improvement of cognitive deficits [26, 27], antipsychotic properties, anxiolytic, antidepressive effects	Asenapine, clozapine, lurasidone, paliperidone, risperidone, ziprasidone, all other atypical antipsychotics (including amisulpride) and haloperidol to a lesser extent

[a] Relationship was assumed if binding affinity measured by Ki value was ≤10 nM/l and defined as being to a lesser extent if Ki values were ≤100 nM/l

EPMS extrapyramidal motor symptoms, *REM* rapid eye movement

important 5-HT-receptor subtypes and their functional effects upon blockade or stimulation are shown in Table 3.

Some of the 'atypical' features of antipsychotics have been related to the stimulation/blockade of serotonin receptor subtypes (see Tables 3, 7) (for review see also MacDonald and Bartolome [25]) [22, 26–28].

2.3 Histamine

The distribution of the four histaminergic receptors in the brain and the functional impact of a blockade or stimulation of the different subtypes are presented in Table 4.

Along with other receptors (5-HT_{2A}, 5-HT_{2C}, α_1, α_2 and M_3), the histamine H_1 receptor seems to be important in the moderation of weight gain [29]. Furthermore, histamine receptors are involved in cognitive processes and cortical activation or sedation.

2.4 Acetylcholine

To date, five muscarinergic receptors have been found in humans. Expression of the receptor subtypes and their postulated functional effects upon blockade and stimulation are presented in Table 5.

The muscarinergic signal transduction has gained importance in the understanding of the pathophysiology of schizophrenia [30–34]. M_1 receptors seem to be important for cognitive functioning [33, 35–37] and development of EPMS (see Table 7). That is why anticholinergic compounds such as biperidene are applied to treat EPMS in schizophrenic patients. However, anticholinergics can also lead to a worsening of cognitive functions, in addition to their peripheral muscarinergic effects like dry mouth, tachycardia, obstipation or urinary retention [33].

2.5 Adrenaline, Noradrenaline (Norepinephrine)

Adrenoreceptors are divided into three families with three to four subtypes each (α_1 adrenoreceptors: α_{1A}, α_{1B}, α_{1D}, α_{1L}; α_2 adrenoreceptors: $\alpha_{2A/D}$, α_{2B}, α_{2C}; and ß adrenoreceptors: β_1, β_2, β_3, β_4) [38].

The central and peripheral distribution of α adrenoreceptors and functional effects upon blockade and stimulation are shown in Table 6.

As a result of a negative feedback mechanism, α_2-adrenoreceptor antagonists work as indirect sympathomimetics: a blockade of the inhibitory α_2 adrenoreceptor results in an increased noradrenergic flux in the synaptic gap. This is used therapeutically to increase male sexual functions and improve depressive mood, and is probably also related to an increase of cognitive functions [39, 40]. The blockade of α_2 receptors is, among other hypotheses, thought to be responsible for the atypical properties of some atypical antipsychotics [8] (see Table 7).

3 Clinical Relevance of Antipsychotic Receptor Binding for Switching and Discontinuing Treatment

3.1 Dopamine Receptors

In animal models, an experimentally induced lack of dopamine results in a postsynaptic hypersensitivity of the nigrostriatal system [41]. Such an increase in hypersensitivity has been thought to be responsible for the occurrence of TD after longer treatment durations with D_2 receptor antagonists, especially with high-potency conventional antipsychotics [42]. After abrupt discontinuation of such substances or switching to quetiapine or clozapine, two compounds only binding at the D_2 receptor for a short period of time [43–45], withdrawal dyskinesia, rebound parkinsonism or rebound akathisia might occur [46].

Davis and Rosenberg [47] postulated that there might be a similar mechanism in the limbic system as a potential consequence of the hypersensitivity of dopamine receptors in analogy to the proposed mechanism of TD. This hypothesis is the basis for the concept of supersensitivity psychosis [3], indicating a compensatory up-regulation and corresponding increase of receptors occurring during antipsychotic treatment.

After an abrupt discontinuation of dopamine antagonists, a rebound psychosis might develop due to the up-regulation of receptors through a higher sensitivity for the physiologically released dopamine—based on this assumption also called supersensitivity psychosis (for review see Moncrieff [12] and Borison [7]). Another hypothesis is that substances that rapidly dissociate from the dopamine receptor (e.g., clozapine or quetiapine) are associated with a higher risk of rebound psychosis [43–45, 48]. Numerous studies exist, in particular for clozapine, reporting rebound psychosis after withdrawal [49–55] (see also Moncrieff for review [12]). The same accounts for reports on dystonias and dyskinesias following cessation of clozapine, which were attributed to be withdrawal emergent [56–58]. The incidence of rapid-onset psychosis (supersensitivity psychosis) after abrupt withdrawal of clozapine was estimated to be as high as 20.1 % in total and 13.2 % within 7 days after discontinuation [12].

Other studies have reported supersensitivity or rebound psychosis following olanzapine withdrawal and during treatment with quetiapine [48, 59]. Generally, data that support the supersensitivity psychosis hypothesis are still lacking and proposed causes speculative [48, 60–63]. A rebound psychosis has to be distinguished from a re-exacerbation or relapse of symptoms induced by

Table 4 Distribution of histamine receptor subtypes and functional effects of blockade or stimulation and their clinical relevance to schizophrenia, bipolar disorder and major depressive disorder

Receptor subtype	Expression	Functional effect if blocked	Functional effect if stimulated	Clinical relevance to schizophrenia, bipolar disorder, major depression	Relevance of these receptors to antipsychotic treatment[a]
H_1 (mainly post-synaptic)	Hypothalamus, limbic system, thalamus, cortex, cholinergic cells in mesopontine tegmentum, locus coeruleus, raphe nucleus [252], nucleus accumbens, cerebellum, area postrema, tractus solitarius	Sedation, sleep induction, decreases food intake [253], reduced anxiety [254]	Cortical activation and arousal, regulation of wake–sleep cycle [255, 256], regulation of appetite and body weight [255, 257], learning, memory, emotions [252, 256, 258], reduced fat accumulation and reduced leptin concentrations [259, 260], regulation of fluid balance [261, 262], increase in blood pressure [263], analgesic effects [264, 265]	Sedation, sleep induction, weight gain, appetite increase	Asenapine, clozapine, olanzapine, to a lesser extent aripiprazole, quetiapine, ziprasidone
H_2 (mainly post-synaptic)	Hippocampus, amygdala, basal ganglia [266, 267], superficial layers of cortex	Decrease of appetite and body weight, reduced anxiety [268]	Decrease in body temperature [269], release of prolactin [270], regulation of weight gain, regulation of fluid balance [261, 262], decrease in heart rate [263], analgesic effects [264, 265]	Reduction in body weight with add-on medication of H_2 antagonists (e.g., nizatidine)	Asenapine, clozapine [271]
H_3 (pre-synaptic)	Autoreceptor [272] and heteroceptors at nucleus accumbens, striatum, olfactory tubercles, substantia nigra, cortex [252]	Increase of firing activity of histaminergic neurons, suppresses feeding [273], antinociceptive action	Inhibition of release and synthesis of histamine [274, 275], inhibition of release of other neurotransmitters (including glutamate [276], GABA [277], noradrenaline (norepinephrine) [278], dopamine [279], acetylcholine [280], serotonin [281], peptides [282]) [255, 283], regulatory effects on wake–sleep cycle, food intake, motility of intestines, perception of pain [284]	Antipsychotic properties (?) [285]	Clozapine (moderate affinity), olanzapine, risperidone, zotepine [271]
H_4	Bone marrow, peripheral immune-competent cells [286]	Reduction of inflammation and neuropathic pain [287, 288]	Accumulation of inflammatory cells	Agranulocytosis (?) [285]	Promethazine, clozapine, olanzapine, risperidone [271, 286]

[a] Relationship was assumed if binding affinity measured by Ki value was ≤10 nM/l and defined as being to a lesser extent if Ki values were ≤100 nM/l

Table 5 Distribution of muscarinergic receptor subtypes in the brain and functional effects of blockade or stimulation and their clinical relevance to schizophrenia, bipolar disorder and major depressive disorder

Receptor subtype	Expression	Functional effect if blocked	Functional effect if stimulated	Clinical relevance to schizophrenia, bipolar disorder, major depression	Relevance of these receptors to antipsychotic treatment[a]
M_1 (post-synaptic)	All cortical layers [289], mainly striatum [290], cortex [291], hippocampus (CA1 pyramidal cells) [292–294], amygdala, thalamus [295]	Impaired vision, photophobia, dry mouth and skin, tachycardia, obstipation, urinary retention, worsening of cognitive dysfunction, improvement of EPMS	Questionable improvement of cognitive dysfunctions in patients with schizophrenia [34]	Anticholinergic delirium with dysfunction of short-term memory, concentration, fear, agitation, increased irritability, aggressiveness, visual/auditory hallucinations, nausea	Clozapine (partial agonist) [296, 297], olanzapine
M_2 (pre- and post-synaptic)	Occipital regions [291, 298, 299], nucleus basalis Meynert [289, 300], striatum [290], hippocampus (presynaptic) [293, 294], amygdala, thalamus [295]	Alteration of synaptic plasticity in hippocampus [301]	Modulation of intrinsic cortical activity [289], function as cholinergic autoreceptor and presynaptic heteroceptor [302]	Involvement in motor dysfunction [301]	Clozapine (partial agonist) [296, 297]
M_3 (pre- and post-synaptic)	Hippocampus [293, 294], subthalamic nucleus [303]	Reduction of cholinergic-dependent inhibition of GABA release and consequent reduction of output from subthalamic nucleus [303]	No data found	Improvement of motor dysfunction [303]	Clozapine (partial agonist) [296, 297]
M_4 (pre- and post-synaptic)	Post-synaptic in putamen (cholinergic interneurons) [289], presynaptic in excitatory synapses [289, 295], hippocampus [293, 294], amygdala, thalamus [295]	Alteration of synaptic plasticity in hippocampus [301]	Modulation of sensoric perception, motor functions, improvement of cognitive processes, memory and concentration, sleep regulation, modulation of pain perception, motivation and mood, antipsychotic effect [34]	Cognitive improvement, antipsychotic properties (?) [34], involvement in motor dysfunction [301]	Clozapine (partial agonist) [296, 297]
M_5	Hippocampus, substantia nigra, ventral tegmental area [304]	No data found	Increases dopamine release [33]	No data found	No data found

[a] Relationship was assumed if binding affinity measured by Ki value was ≤10 nM/l and defined as being to a lesser extent if Ki values were ≤100 nM/l

EPMS extrapyramidal motor symptoms

Table 6 Distribution of adrenergic receptor subtypes and functional effects of blockade or stimulation and their clinical relevance to schizophrenia, bipolar disorder and major depressive disorder

Receptor subtype	Expression	Functional effect if blocked	Functional effect if stimulated	Clinical relevance to schizophrenia, bipolar disorder, major depression	Relevance of these receptors to antipsychotic treatment[a]
α_1 (α_{1A}, $_{1B}$, $_{1D}$ and $_{1L}$)	Central: cerebellum (region-specific Purkinje cells) [305]	Enhanced reactivity to new situations (α_{1B} knock-out mice) [306], impairment of motor function [307], antipsychotic effects [308–310]	Enhancement of stimulus-evoked signals [305, 311], impairment of prefrontal cortical functions [312, 313], enhancement of long-term memory consolidation of emotionally charged material [314–316]	Modulation of certain behaviours such as reaction to novelty and exploration (via α_{1B} receptors) [38]	Asenapine, clozapine, iloperidone, quetiapine, risperidone, sertindole, ziprasidone, to a lesser extent lurasidone, paliperidone, olanzapine, haloperidol
	Peripheral: predominantly postsynaptic on blood vessels, smooth muscles of bladder, prostate [317], urethra, vas deferens [318, 319]	Contractions of arteries [320]	Rise in blood pressure, contraction of genitourinary organs [317–319], prolongation of refractory phase, mydriasis, increase in glycogenolysis, increased expression of LDL receptors, decrease of cholesterol synthesis	Orthostatic dysregulation, sedation, dizziness, reflex tachycardia, ejaculatory dysfunctions, urinary retention, nasal congestion	
$\alpha_{2A/D}$[b]	Presynaptic on neurons in cerebral cortex, postsynaptic in prefrontal cortex [308], cerebellum (all neurons) [305]	Increased noradrenergic flux, improves depressive mood, might contribute to atypical properties of antipsychotics, increase of adipose tissue without weight gain, increased novelty seeking [321], impairment of working memory performance [322]	Reduced attention to novel stimuli [323], anesthetic and sympatholytic responses [324], modulation of transmitter release [325, 326], auto-inhibition, inhibition of transmitter release, analgesia [327], sedation [327], anxiolytic [327], central lowering of blood pressure [327], hypothermia, vasoconstriction [320], relaxation of gastrointestinal system, decrease of lipolysis, release of insulin, stimulation of platelet aggregation [328]	Sympatholytic actions [324] or indirect sympathomimetic effect of antagonists, modulation of spatial working memory [329, 330]	Asenapine, risperidone, to a lesser extent aripiprazole, clozapine, lurasidone, paliperidone
α_{2B}	Postsynaptic neurons of vegetative and CNS, cerebellum (all neurons) [305], smooth muscles	No data found	Short-term hypertensive response [331]	No data found	Asenapine, risperidone, to a lesser extent clozapine, quetiapine
α_{2C}	Post-synaptic neurons of vegetative and CNS, cerebellum (region-specific Purkinje cells) [305], smooth muscles	Enhanced startle response and shortened attack latency in knock-out mice [332], increases catecholamine release [308], alleviation of EPMS [333], possible improvement of cognitive deficits [334, 335]	Hypothermia [336], modulation of transmitter release [325, 326], enhancement of dopamine function in striatum [308]	Anxiolytic effects, improvement of EPMS [333], improvement of cognitive deficits [334, 335]	Asenapine, clozapine, risperidone, to a lesser extent aripiprazole, iloperidone, lurasidone, olanzapine, quetiapine, ziprasidone

[a] Relationship was assumed if binding affinity measured by Ki value was ≤10 nM/l and defined as being to a lesser extent if Ki values were ≤100 nM/l

[b] The α_{2D} is an orthologue of the α_{2A} receptor in rats

EPMS extrapyramidal motor symptoms, *LDL* low-density lipoprotein

Table 7 Overview of receptor interactions for possible explanation of clinical effects of psychopharmacological drugs relevant for the treatment of schizophrenia

Receptor interaction	Pharmacological characteristic	Clinical effect
D_1–D_2	Simultaneous blockade results in functional disinhibition of dopaminergic neurons and counteraction of D_2 blockade	Reduction in motor adverse effects, improvement in motivation and cognitive functioning
D_2–D_3	Simultaneous blockade results in functional disinhibition of dopaminergic neurons and counteraction of D_2 blockade [222]	Reduction of motor adverse effects
5-HT_{1A}–5-HT_{2A}	Stimulation of 5-HT_{1A} results in hyperpolarization of neurons resulting in oppositional effects to stimulation of 5-HT_{2A} receptors; 5-HT_{1A} agonism and 5-HT_{2A} antagonism exert synergistic effects on hyperpolarization of pyramidal neurons in cortex and hippocampus [337]	Antipsychotic properties [26]
5-HT_{1A}–D_2	Stimulation of 5-HT_{1A} counteracts D_2 blocking action in striatum [238–241]	Reduction of motor adverse effects
5-HT_{2A}–D_2	High affinity for 5-HT_{2A} and low affinity for D_2 receptors and concurrent blockade leads to higher dopaminergic tonus in striatum [243–246]	Questionable basis for 'atypical' properties
5-HT_{2C}–D_2	Simultaneous blockade results in counterregulation of dopaminergic blockade in tuberoinfundibular pathway	Reduction in prolactin levels
5-HT_3–D_2	Modulation of mesolimbic and mesocortical dopamine effects; 5-HT_3 antagonists reverse dopamine-mediated behaviours [338]	Antipsychotic effect
M_1–D_2	Concurrent blockade attenuates increased cholinergic tonus in striatum, resulting from inhibition of the dopaminergic tonus [33]	Reduction in motor adverse effects
α_2–D_2	α_2-Adrenoceptor antagonists increase dopamine output in the medial prefrontal cortex [40]	Augmentation of antipsychotic effects
D_1–α_1–5-HT_{2A}	Noradrenergic stimulation during stress in prefrontal cortex interacts with dopaminergic stimulation of D_1 receptors in PFC, α_1 and 5-HT_{2A} blockade attenuate these effects [308]	Stress-mediated cognitive impairment of working memory in prefrontal cortex and improvement via α_1 and 5-HT_{2A} blockade [308]

withdrawal stress. The onset of psychotic symptoms in the case of re-exacerbation or withdrawal stress-induced relapse usually occurs more promptly after the reduction or discontinuation of antipsychotic medication [12], whereas for rebound psychosis the current literature reports a time frame of around 6 weeks after discontinuation of oral medication and 3 months after depot compounds [1]. However, differentiation is not always easy, and the stability of disease in a particular patient also has to be taken into account. It should also be borne in mind that, in the case of rebound psychosis, symptoms should subside faster on restarting medication compared with a relapse of the underlying disease. In addition, rebound psychosis, e.g., after discontinuation of clozapine might be accompanied by other withdrawal symptoms like nausea, vomiting, insomnia, diarrhoea, agitation, headache or sweating, indicative of e.g., cholinergic rebound [6].

A positive effect of changing treatment from a substance with high D_2-receptor blockade to agents with lower D_2-receptor affinity or partial agonistic properties is the normalisation of increased prolactin levels and concurrent sexual dysfunction.

3.2 Serotonin Receptors

There are almost no data available on specific withdrawal or rebound phenomena associated with the different serotonin receptors. A rebound-induced hyperthermia has been described for treatment with olanzapine. It is still unclear which receptors are responsible for this, but serotonin receptors might be involved [64].

A switch from an atypical antipsychotic with higher 5-HT_{2A}-receptor affinity to a typical antipsychotic in higher doses might result in a loss of the effect on negative or cognitive symptoms and development of EPMS.

Positive effects can be attained when switching treatment from e.g., clozapine or olanzapine to risperidone, aripiprazole or ziprasidone, as this might result in a loss of body weight due to the lower blockade of 5-HT_{2C} receptors.

3.3 Histamine Receptors

In the case of high body mass index (BMI) or lipid disturbances [65] associated with blockade of H_1 receptors, patients may benefit from switching to more weight-neutral antipsychotics (e.g., aripiprazole or ziprasidone) (see also review by Buckley and Correll [65]). Apart from positive effects on weight, discontinuing antipsychotics with high H_1-receptor affinity might result in a decrease of sedation or rebound insomnia [8, 65, 66].

3.4 Muscarinergic Receptors

A longer-standing blockade of muscarinergic receptors results in a cholinergic supersensitivity and might evoke rebound phenomena when treatment is abruptly discontinued [7]. Thus, discontinuing substances with strong anticholinergic properties (e.g., clozapine or olanzapine) might result in a cholinergic rebound. Symptoms include nausea, vomiting, increased sweating or sleeping problems, or other, flu-like symptoms [11]. However, also agitation, fear or hallucinations can emerge resembling a newly developing psychotic episode. In the absence of vegetative symptoms like nausea or vomiting, the psychiatric symptoms of cholinergic rebound are not distinguishable from a withdrawal stress-enhanced dopaminergically mediated psychotic syndrome.

A cholinergic rebound might also occur when anticholinergic treatment (e.g., biperidene) or treatment with a lower potency antipsychotic (e.g., levomepromazine) are discontinued [2, 11].

3.5 Adrenoreceptors

Not much is known about the functional impact of a long-lasting α_1- or α_2-adrenoreceptor blockade by antipsychotics. However, it can be assumed that, during treatment with an antipsychotic drug having α_1/α_2-antagonistic properties, a compensatory progression or an increase of sensitivity of the blocked receptors might emerge.

Correspondingly, after the abrupt discontinuation of a relevant antipsychotic or after switching treatment to an antipsychotic without adrenoreceptor-antagonistic properties, a temporary sympathotonic reaction with an increase in blood pressure or fear might occur [67–69]. From a clinical point of view the worsening of negative symptoms and the evocation of rebound phenomena might be explained by the increase in symptoms of fear [67]. A rebound-induced hyperthermia has been described for clozapine, probably mediated by α_1 adrenoreceptors [6]. The exact mechanisms are not yet fully understood [6].

4 Findings from Trials of Switching Strategies

In the above sections, particular symptoms and difficulties potentially occurring during the switch or discontinuation of antipsychotic treatment have been described for all receptors. However, whether these theoretical implications really occur in clinical practice, how often rebound and withdrawal phenomena are encountered and whether certain switching strategies might be associated with higher frequencies of events becomes more evident when the results of clinical switching trials are considered.

There are principally four strategies when switching antipsychotic treatment [65]:

1. Slowly up-titrating the new compound until the therapeutic dose is reached and afterwards slowly reducing the previous drug with or without plateau phase (‘plateau cross-taper switch’).
2. Abruptly switching treatment without titration (‘abrupt switch’).
3. Slowly up-titrating the new compound with subsequent abrupt discontinuation of the previous drug (‘ascending taper switch’).
4. Slowly discontinuing the previous compound with an abrupt start of the new drug at a therapeutic dose (‘descending taper switch’).

Correll subdivides these switching strategies into further groups (ascending and descending taper switch with a plateau phase and plateau switch with abrupt initiation and discontinuation of compounds) so that altogether eight different switching strategies are available [70]. Several studies investigating switching from one atypical antipsychotic to another have been conducted (for review see Edlinger et al. [71]). In Sects. 4.1–4.11, we review some of the pertinent findings from switching trials.

For this purpose we conducted a literature search using MEDLINE and EMBASE databases for original research and review articles published in English or German between January 1995 and January 2012. The search terms included ‘atypical antipsychotics’, ‘switching strategies’, ‘each compound name (e.g., olanzapine) AND switching’, ‘each compound name AND each of the remaining compound names’, ‘each compound name AND each of the terms withdrawal, rebound, supersensitivity’. Additional articles were retrieved from citations of the articles identified in the initial search and included if eligible. For the latest approved compounds (asenapine, iloperidone, lurasidone) additional information was obtained by accessing the http://www.clinicaltrials.gov database entering the compound name as the search term. Articles published in peer-reviewed journals were included, meeting abstracts were not. Only case reports or clinical trials of patients with schizophrenia or schizoaffective disorders were

considered. Only articles reporting on either withdrawal/rebound phenomena or switching to a defined compound were eligible for the following antipsychotics: amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, sertindole and ziprasidone. As the literature search retrieved no published switching trials to any of the latest approved compounds (asenapine, iloperidone, lurasidone), studies reporting on initiating treatment with any of these compounds and leading to later approval of the substances were also included. Switches to treatment with clozapine were not included given the restrictions on the use of the drug (second-line treatment only, mainly for refractory schizophrenia). The most important findings are summarized in Sects 4.1–4.11 in alphabetical order for the agent switched to. An overview of relevant studies can be found in Tables (a)–(h) [Online Resource 1].

4.1 Switch to Amisulpride

Only two studies investigated a switch to amisulpride from other atypical antipsychotics. The number of investigated patients ranged from 46 to 570 [72, 73]. Patients switched to amisulpride showed a decrease in weight, lipid and glucose levels, diastolic blood pressure and pulse rates using a cross-taper strategy [72]. Overall symptomatology and EPMS scores did not improve, seven patients dropped out because of disease exacerbation, and prolactin levels increased [72].

Until further studies are available, we recommend a cross-taper switch strategy when switching to amisulpride. Patients switched to amisulpride may profit from improvement in weight and lipid metabolism, but may develop prolactin increase depending on the pre-switch compound. Because of the lack of antihistaminergic or anticholinergic properties of amisulpride, switching from for example clozapine or olanzapine may warrant use of anticholinergic and sedative substances during the switching process.

4.2 Switch to Aripiprazole

Patients were switched from olanzapine, risperidone or other antipsychotics to aripiprazole (number of patients 7–292) [74–89] mostly because of AEs. There was generally good tolerability regardless of switching strategy (abrupt, descending taper, cross-taper) over 1–12 weeks. However, some of these studies were sponsored by the manufacturer, and results have to be considered with caution in these cases. Notably, in a pilot study of 15 overweight patients switching from different antipsychotics to aripiprazole with a descending taper switch strategy, five patients showed exacerbation or fear of symptom worsening during the 14-day switching period. Four of these patients were treated with clozapine or olanzapine [78]. In one study, a patient committed suicide following symptom exacerbation after an abrupt switch from long-acting injectable risperidone to aripiprazole [90].

By contrast, there are some reports of patients being successfully switched from clozapine to aripiprazole [91, 92] (for review see also Kuloglu et al. [93]). *N*-desmethylclozapine, the primary active metabolite of clozapine, and aripiprazole both share partial agonism at D_2/D_3 receptors and thus partial agonism at these receptors remains during switching of clozapine to aripiprazole. This was suggested as the basis for successful switching of both compounds [92]. A study examining different switching strategies found no difference between strategies switching from typical or atypical antipsychotics to aripiprazole, but showed that duration of illness and type of prior treatment (typical vs. atypical) were determinants of successful switching [80]. TEAEs in these studies like insomnia, somnolence, nausea, vomiting or diarrhoea were usually attributed to aripiprazole and were not discussed as potential withdrawal phenomena, e.g., cholinergic rebound after switch from clozapine [78, 86, 88, 94].

A study investigating three strategies of switching to aripiprazole showed better treatment outcome in patients with gradual discontinuation over 4–6 weeks of prior medication compared with abrupt switch. Interestingly, patients with a milder form of disease showed the worst outcome [83, 84]. However, gradual initiation or a fixed-dose regimen of aripiprazole did not result in statistically significant different rates of discontinuation due to AEs in the case of gradually descending titration of risperidone [85]. Depending on the stability and physical status of patients, two different initiation regimens of aripiprazole have been proposed by Mago [95].

See Table (b) [Online Resource 1] for more detailed information.

Generally, rebound or withdrawal symptoms were not reported in most of the above-mentioned studies. Patients did profit from a decrease in weight and prolactin levels and improvement in lipid profiles, overall symptomatology and sexual dysfunction [82]. Switching from clozapine or olanzapine seems to be associated with an increased risk of rebound psychosis. A descending taper switch, preferentially with a plateau phase over a time span of 4–6 weeks depending on prior medication is recommended when switching to aripiprazole. This recommendation is based on the long half-life of aripiprazole, although some studies found no differences in TEAEs comparing switching scenarios from diverse compounds to aripiprazole [74, 85, 89]. Even though aripiprazole has the highest affinity at the D_2 receptor and will displace all other atypical antipsychotics from the D_2 receptor, it also exerts about 30 % intrinsic activity. Therefore, higher

occupancy levels are needed to result in a comparable antipsychotic effect [9, 96].

4.3 Switch to Asenapine

To date, no specific switching trials have been performed investigating switching strategies to asenapine; however, product labelling recommends minimizing the overlapping of antipsychotic treatment and states that immediate or gradual discontinuation of prior antipsychotic medication is acceptable depending on the individual patient [97]. In a long-term treatment study, Kane et al. [98] reported that 548 of 700 patients treated in the open-label phase of the study were switched from previous antipsychotic treatment with a mean duration of 12.6 ± 6.5 days. Studies showed TEAEs with frequencies ≥5 % in the form of insomnia, somnolence, sedation, nausea, anxiety, agitation, parkinsonism, akathisia, headache, vomiting, constipation, (worsening of) psychosis, hypertension (older patients), dizziness, dyspepsia, asthenia (older patients), upper respiratory tract infection, urinary tract infection (older patients), pain, oral hypoesthesia and dry mouth [98–103]. Weight increased with asenapine but to a lesser extent compared with risperidone or olanzapine, but not to haloperidol [98–103]. Prolactin levels were only marginally higher compared with placebo (9 vs. 2 % of patients with post-baseline levels ≥2 times above the upper limit of normal) [102], and even dropped in the study of Kane et al. [101]. In the long-term study by Kane et al., patients were randomized to double-blind treatment with asenapine or placebo after open-label treatment with asenapine and AEs were assessed at 7, 14 and 42 days post-randomization to address potential symptoms from withdrawal from asenapine. The authors found no AEs to be definitely associated with asenapine withdrawal [98]. However, whether any TEAEs might be attributed to discontinuation of previous medication was not discussed. In a recent study, patients with predominantly negative symptoms were started on asenapine 5–10 mg twice daily or olanzapine 5–20 mg once daily and tapered off their previous medication over 4 weeks in parallel. Prior medication included risperidone, olanzapine, quetiapine, haloperidol and aripiprazole [100]. EPMS-related AEs occurred more often in the asenapine group compared with the olanzapine group, weight gain and dry mouth occurred more often in the olanzapine group [100]. Further information on trials conducted with asenapine retrieved from http://www.clinicaltrials.gov can be found in a review by Citrome [104]. According to product labelling, orthostatic hypotension and syncope may occur especially during up-titration of asenapine and is reported to be related to α_1-receptor antagonistic properties [97].

Therefore, based on the AE and receptor-binding profile, nausea, vomiting, dizziness and insomnia might be due to rebound phenomena in the case of switching from agents with high muscarinergic M_1-receptor affinity to asenapine. This assumption is corroborated by differences in rates of nausea and insomnia occurring more often in the group switched to asenapine compared with patients switched to olanzapine in the long-term study by Buchanan et al. [100]. Switching to asenapine might be advantageous with respect to weight gain, metabolic disturbances or prolactin increase; however, trials investigating switching strategies are necessary to confirm such hypotheses.

4.4 Switch to Iloperidone

The database search retrieved no specific switching trials. Studies investigating efficacy and tolerability of iloperidone reported on switching from other antipsychotics to iloperidone with a washout period of 1–3 days [105, 106] or with abrupt discontinuation of the previous compound and up-titration of iloperidone thereafter without washout [107]. An up-titration of iloperidone over a few days is recommended according to the product label because of the risk of orthostatic hypotension after initiation. One of the metabolites has a very high reported affinity for the α_1 receptor (P95; Ki: 4.7) [108]. TEAEs comprised orthostatic hypotension, dizziness, dry mouth, nausea, headache, nasal congestion, somnolence, insomnia, anxiety, agitation, tachycardia, dyspepsia and weight increase [105–107, 109]. Five patients experienced delusions, psychotic disorder or schizophrenia [109]; by contrast, EPMS scores and akathisia decreased [107, 109].

In the clinicaltrials.gov database, one study (i-FANS; NCT01207414A) is listed addressing two switch approaches to iloperidone in schizophrenia patients currently treated with risperidone, olanzapine or aripiprazole with the aim of assessing efficacy, safety and tolerability, but results are not yet available.

To conclude, although results of switching strategies are lacking, it might be advisable to use cross-titration with switch strategies to moderate the risk of symptomatic relapse during initial up-titration of iloperidone. The moderate affinity for the H_1 receptor and lack of affinity for M_1 receptors warrants further precautions in order to avoid histaminergic or cholinergic rebound phenomena [110]. A switch to iloperidone might be most favourable for patients experiencing EPMS, akathisia or sedation with prior medication. However, unless trials addressing specific strategies for switching from different antipsychotics are performed these recommendations remain speculative.

4.5 Switch to Lurasidone

According to the clinicaltrials.gov database two studies investigating switching from other antipsychotics to

lurasidone have been performed (SWITCHCore; NCT01143077 and Switch Ext; NCT01143090); however, the results are not reported yet. In a systematic review, Citrome summarized data on efficacy and safety of the trials leading to approval [111]. Most TEAEs in phase II and III studies occurring at frequencies ≥5 % comprised akathisia, nausea, sedation, vomiting, somnolence, headache, insomnia, anxiety, agitation, dyspepsia, constipation, restlessness, parkinsonism, tremor, dystonia and salivary hypersecretion [111–115]. Some AEs e.g. somnolence, akathisia or parkinsonism seemed to be dose related, which makes it less likely to be rebound phenomena [116]. Overall weight gain and changes in metabolic parameters were comparable to placebo. A modest prolactin increase was observed in some studies [111, 113, 116]. Psychotic symptoms as emerging AEs were reported in up to 3.4 % of patients [116].

In summary, despite the lack of results from switching trials a change of medication to lurasidone might be advantageous in terms of normalization of metabolic parameters and weight. Depending on the pre-switch compound, rebound insomnia might occur. However, this remains to be elucidated in trials specifically addressing these issues.

4.6 Switch to Olanzapine

The number of patients in studies that investigated a switch to olanzapine ranged from 19 to 1,267 and included in- and outpatients; reasons for the switch were either lack of efficacy, AEs or patient request [117–133]. Different switching strategies were chosen including crossover with descending taper, plateau cross-taper and abrupt strategies. The time span of switching ranged from abrupt to several weeks. Studies sponsored by Eli-Lilly more generally reported good tolerance of switching from clozapine, risperidone or other antipsychotics, and improvement of symptoms and quality of life [118–121, 126, 127, 129, 130]. In some studies potential signs of withdrawal were noticed including withdrawal dyskinesia in patients switched from clozapine [122] and new onset of headache, seizures, anxiety, dizziness or insomnia, which were discussed as being attributable to discontinuation of haloperidol or anticholinergic drugs [117]. Also, akathisia, dyskinesia and movement disorders were reported as rebound phenomena [117]. In one study, seven patients switched from clozapine to olanzapine required hospitalization due to exacerbation of symptoms; however, these were not discussed as rebound psychosis [122]. Furthermore, in case reports of therapy-refractory patients switched from clozapine, diaphoresis, hypersialorrhea, bronchial obstruction, agitation, anxiety and enuresis were reported as potential signs of withdrawal [134]. Patients switched from typical antipsychotics or risperidone benefited more from a descending taper switch with immediate initiation of 10 mg of olanzapine followed by gradual discontinuation of the previous medication compared with ascending taper switch or abrupt discontinuation of prior treatment [126].

Please see Table (c) [Online Resource 1] for results of other studies.

To put it in a nutshell, patients switched from typical antipsychotics usually had benefit in core symptoms and EPMS reduction, but showed weight gain. Patients switched from risperidone had a further decrease in prolactin levels [125]. Olanzapine should be introduced in therapeutic doses and previous agents gradually tapered.

4.7 Switch to Paliperidone

Data on TEAE switching to paliperidone is still limited. Short- and long-term studies of paliperidone palmitate reported on AEs with frequencies of ≥5 % comprising akathisia, dizziness, EPMS, injection-site reactions, somnolence, sedation, insomnia, anxiety, agitation, headache, nasopharyngitis, schizophrenia and psychotic disorder [135–139]. Furthermore, moderate weight gain was observed [137, 140, 141]. Prolactin levels increased compared with placebo [140]. Both weight gain and prolactin increase were found to be dose related [140]. Switching regimens from oral or injectable antipsychotics to paliperidone palmitate has been extensively described elsewhere [142, 143]. According to product labelling oral antipsychotics can be discontinued after initiation of paliperidone palmitate [144]. A gradual cross-taper from oral antipsychotics with the potential of cholinergic rebound may seem clinically advisable, but has not been specifically studied [143]. One case report described a switch to oral paliperidone (3 mg) from aripiprazole (5 mg) that resulted in improvement of oral dyskinesias. Higher 5-HT_{2A} antagonism of paliperidone over aripiprazole was discussed as a possible reason by the authors [145]. Another case report described the development of neuroleptic malignant syndrome in a patient switched from oral risperidone to oral paliperidone and back to oral risperidone. The authors discussed the low initiation dose of paliperidone (3 mg) when switching from 4 mg of risperidone as the reason for the observed effects and emphasized adequate dosing in case of switching to oral paliperidone [146] (see also Tables (f) (h) [Online Resource 1]).

In summary, patients switched to paliperidone may benefit from low propensity of anticholinergic AEs and moderate sedation and weight gain compared with for example olanzapine or quetiapine. Until further elucidated in clinical trials, cross-taper strategies switching from antipsychotics with higher muscarinergic affinity seem to be advisable.

4.8 Switch to Quetiapine

Several trials were conducted investigating the safety and efficacy of a switch to quetiapine immediate release ($n = 16$–164) [147–150] or extended release ($n = 477$) [151, 152]. Studies of a switch to quetiapine IR used cross-taper switch strategies of 1–4 weeks. Patients switching from typical antipsychotics or risperidone improved in EPMS scores, but showed weight gain. Patients switched from olanzapine due to weight gain or BMI increase lost some weight, but did not show alterations in symptoms. Other studies using, for example, a cross-titration within 4 days found improvement of symptoms, EPMS scores and improvement in prolactin levels. TEAEs in these studies included tremor, akathisia, EPMS, psychosis and exacerbation of psychosis, sedation or dizziness [151]. Patients showing worsening of psychosis had previously higher levels of Positive and Negative Syndrome Scale (PANSS) positive scores [150]. For further details see Table (d) [Online Resource 1].

To conclude, patients switched to quetiapine may profit from reduction in EPMS and prolactin levels or weight reduction in the case of olanzapine or clozapine being the previous compound. In most other cases weight may increase. When switching from conventional antipsychotics, patients should be carefully monitored for withdrawal dyskinesias or rebound psychosis. Cross-taper strategies are recommended.

4.9 Switch to Risperidone and Risperidone Long-Acting Injectable

The number of patients in studies reporting a switch to risperidone ranged from 10 to 684 [153–159]. In outpatients switched from olanzapine due to lack of efficacy or to AEs, withdrawal symptoms including nausea, vomiting, agitation and movement disorders were noticed, along with aggravated psychosis or anxiety in those patients switched abruptly compared with patients with a taper switch strategy. Furthermore, a mean reduction in standing diastolic blood pressure possibly related to cholinergic rebound was observed [153]. Among treatment-resistant patients switched from clozapine ($n = 10$) with a cross-taper strategy none improved, five patients showed exacerbation of psychosis and withdrawal symptoms were observed [154].

Patients switched from typical antipsychotics showed improvement in symptoms, quality of life, service utilization and use of anticholinergics [156, 160], and patients switched from olanzapine showed amelioration of a previous metabolic syndrome [157]. In a study investigating switching from conventional antipsychotics to risperidone, regression analyses showed that the dose of prior medication at baseline was associated with successful switching. The authors discuss the fact that symptoms associated with withdrawal might occur more frequently in patients with higher initial doses of typical antipsychotics [158].

The studies investigating a switch to risperidone long-acting injectable indicated for example improvement in cognitive function, insight and social functioning and found TEAEs comprising headache, relapse (7.7 % mostly within three weeks), insomnia, disease exacerbation, anxiety and movement disorders (akathisia, tremor), weight gain and hyperprolactinemia (see Tables (e) and (f) [Online Resource 1] for detailed information). Some of these symptoms might have been rebound phenomena, but this was not discussed by the authors [90, 161, 162]. Switching from depot formulation of typical antipsychotics led more often to symptom exacerbation than switching from oral formulations (9.5 vs. 3.1 %) [162].

For clinical practice, taper-switch strategies over about 2 weeks are recommended [153]. Patients may benefit from weight reduction or amelioration of metabolic parameters in the case of switching from clozapine, olanzapine or quetiapine, but may experience worsening of psychosis. Development of insomnia, anxiety and EPMS may be related to rebound phenomena. Clinicians should carefully monitor patients switched from other depot-medication.

4.10 Switch to Sertindole

There are only sparse data on TEAE in the case of switching to sertindole. Most TEAEs comprise headache, insomnia, rhinitis/nasal congestion, male sexual dysfunction and moderate weight gain [163]. A study comparing metabolic changes of risperidone and sertindole found comparable numbers of patients experiencing weight gain, changes in lipid plasma levels and developing metabolic syndrome [164].

A patient switched from clozapine to sertindole experienced severe psychotic symptoms that subsided after re-initiation of clozapine. The authors recommended cross-taper switching strategies and careful monitoring of withdrawal phenomena while switching from clozapine to sertindole [165]. Another case report discussed amelioration of rebound insomnia in a patient discontinuing clozapine after initiation of treatment with sertindole and quetiapine [166]. Patients with TD switched from conventional antipsychotics to sertindole were found to improve in movement disorders [167].

Sertindole is considered a second-line treatment option in schizophrenic patients given its overall higher cardiac mortality [168]. Considering these treatment restrictions, patients switched to sertindole may profit from its low propensity of inducing EPMS and sedation. Clinical studies assessing best switching strategies are lacking to date.

Careful monitoring of rebound insomnia and rebound dyskinesias while switching to sertindole seems to be advisable.

4.11 Switch to Ziprasidone

Several large trials (primarily sponsored by Pfizer) report on switching from typical antipsychotics, olanzapine, risperidone or quetiapine to ziprasidone involving in- and outpatients (n = 19–312) due to lack of efficacy or AEs [169–177]. The trials compared different switching strategies and found overall improvement in EPMS scores, weight, lipid profiles, prolactin levels, sexual dysfunction and cognitive function. TEAEs included insomnia, somnolence, anxiety, nausea, dizziness, headache and asthenia. Withdrawal or rebound phenomena were usually not reported or discussed. Insomnia after a switch from olanzapine or quetiapine was often attributed to ziprasidone (see Table (g) [Online Resource 1] for further details).

A review by Rossi et al. [178] on the available literature regarding switches to ziprasidone recommends a plateau cross-titration strategy. To minimize rebound and withdrawal effects the concurrent use of benzodiazepines, anticholinergics or β-blockers was proposed to be of benefit for the patients depending on the antipsychotic prior to the switch. Switching from conventional antipsychotics appeared to be slightly advantageous when done using a slow taper strategy of prior medications; however, differences between switching strategies were only subtle and not conclusive. Still, some strategies might lead to a greater number of rebound dyskinesias than others [176]. Other authors found no differences when comparing switching strategies, including abrupt discontinuation or fast and slow descending taper switch [177].

In general, a major limitation of a considerable number of switching trials is the open-label character of many studies or the fact that they are only case reports. However, the quality of studies and the number of included patients have increased in recent years.

5 Conclusions for Clinical Practice

5.1 Reasons for Switching Antipsychotic Medication

There are several reasons for switching antipsychotic medication, including insufficient efficacy as well as AEs such as EPMS, weight gain, increase in prolactin, sexual dysfunction, severe sedation or ECG alterations. However, switching medication carries the risk of, in general, greater resource utilization and a higher likelihood of patients discontinuing the newly assigned medication compared with patients who stayed on an initial assigned treatment [179, 180]. It remains to be elucidated whether switching medication always results in better outcome for the patients. Indeed, analyses of the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) trial found no differences between "switchers" and "stayers" [181]. Therefore, physicians should (1) consider risks and benefits of switching medication, and (2) choose the safest switching strategy for the envisioned medication.

5.2 Withdrawal and Rebound Syndromes Associated with Switching

Summarizing the findings from clinical trials and case reports, switching antipsychotic medication might be associated mainly with rebound psychosis, withdrawal dyskinesias, rebound insomnia and rebound cholinergic syndrome. An aid in assessing whether TEAEs are due to withdrawal/rebound phenomena or related to the initiated drug might be the time point of occurrence of the event. Generally, clinicians should be alert regarding the occurrence of vegetative rebound symptoms or cholinergic rebound within the first few days after the switch or discontinuation of treatment. Rebound akathisia might appear within the first few days, whereas rebound parkinsonism usually emerges after a week and rebound dyskinesia might only become apparent within a month.

However, the time-course of TEAEs comprising these aforementioned symptoms is quite similar and may not be easy to distinguish. Akathisia has been found to occur in 75 % of all cases after 3 days of treatment [182]. The same accounts for parkinsonism, which may develop within days or weeks after initiation of antipsychotic treatment and for dyskinesias, as chronic dyskinesias may also develop within a few weeks [183, 184]. To further discriminate whether any of these AEs are related to the discontinued drug a re-exposure might help, as the symptoms should subside faster in the case of being related to the former substance when switching antipsychotics. However, this has not been subject to systematic research and knowledge is still limited.

5.3 Types of Switching Strategies

As mentioned in Sect. 3, switching strategies include '(plateau) cross-taper switch', 'abrupt switch', 'ascending taper switch' and 'descending taper switch'. As a basic principle, the half-life can be considered as an orientation in choosing the appropriate switching strategy. A more rapid switch of treatment is less problematic when switching from antipsychotics with a longer half-life, although precautions have to be taken if the post-switch antipsychotic has a longer half-life (for review see Correll [9]). Through this strategy the individual's physiology is

able to adjust to the changed treatment conditions and a supersensitivity or desensitisation can be normalized again. This of course should not exclude an abrupt withdrawal in the case of for example agranulocytosis resulting from treatment with clozapine.

When treating patients in an outpatient clinic cross-over strategies are often preferred, limiting possible rebound phenomena [126, 153, 185]. Since a cross-over design requires the concurrent intake of at least two different antipsychotics, specific instructions and intensive psychoeducation is recommended. Otherwise, a complex dosing regimen might decrease the patients' compliance [70]. Furthermore, the potential risk of TEAEs resulting from simultaneous intake of at least two antipsychotics has to be weighed against the risk of rebound phenomena in choosing cross-over strategies. In this scenario pharmacokinetic interactions of antipsychotics have to be considered. In this review, we focused on pharmacodynamic correlations based on receptor affinities. For the interested reader we recommend Edlinger et al. [71]. and Correll [9] for review of potential problems when switching antipsychotics because of pharmacokinetic interactions. In the case of polypharmacy involving potent inhibitors or inductors of the cytochrome P450 isoenzymes like certain antidepressants (e.g. fluoxetine, paroxetine, fluvoxamine) or mood stabilizers (e.g. carbamazepine, valproic acid), the situation becomes even more complicated [186–188].

5.4 Strategies to Avoid Withdrawal and Rebound Syndromes

Different strategies are available to prevent withdrawal/rebound syndromes during the switching of antipsychotic treatment. These include the application of benzodiazepines, antihistaminics, anticonvulsants, anticholinergics, β-blockers or the prolongation of the switching phase [65, 178]. The use of anticholinergic substances may help to avoid cholinergic rebound [189]. To lower the risk of rebound insomnia when treatment with an antipsychotic having high H_1-receptor affinity is discontinued, the additional application of benzodiazepines or other sedatives might be a suitable strategy. We further recommend informing patients about these rebound phenomena, since insomnia might also be the initial symptom of a psychotic re-exacerbation.

Generally, switching antipsychotics slowly with an overlapping phase of both antipsychotics applied ('plateau cross-taper') can be recommended [190, 191]. However, the evidence for this strategy is still not fully based on double-blind studies with adequate control groups, and other authors may come to different conclusions [192, 193].

Another strategy to prevent rebound phenomena is to adequately plan where and when to switch the patient's treatment. If the clinician expects the patient to have difficulties with changes in the treatment regimen or to develop symptoms like insomnia, fear or agitation, it might be helpful to admit the patient to a day hospital or even to recommend inpatient treatment. This might help improve the monitoring and treatment of potential rebound symptoms. Furthermore, other psychopharmacological compounds can cause rebound phenomena, a fact that should be considered in clinical practice, because many patients with schizophrenia are no longer only treated with antipsychotics. Also, a benzodiazepine withdrawal might result in the occurrence of psychotic symptoms and should not be mistaken for an exacerbation of the psychiatric illness itself.

5.5 Switching from/to Different Antipsychotics

Rebound psychosis or stress-related exacerbation of psychosis during switching is probably considered the most problematic withdrawal/rebound phenomenon. According to the reviewed literature, exacerbation of psychosis occurred most often when switching from clozapine/olanzapine to other atypical antipsychotics [74, 78, 154]. We would therefore recommend a gradual and slow discontinuation when switching treatment with clozapine or olanzapine to substances without a muscarinergic receptor affinity, respectively. Furthermore, patients abruptly discontinuing clozapine seem to need higher doses for remission after exacerbation of disease and also show a deterioration in the quality of remission [194]. Patients switched from clozapine or olanzapine to risperidone or aripiprazole seem to be particularly vulnerable to rebound psychosis. Thus, slow cross-taper strategies, optionally including concurrent use of benzodiazepines or anticholinergic compounds might be advisable. This may also hold true for amisulpride, asenapine, iloperidone, lurasidone, paliperidone and ziprasidone, but so far there are no data from clinical trials to support this notion.

Table 8 gives a summary of potential TEAEs that might result from withdrawal or rebound phenomena during switching antipsychotics. Only compounds are addressed where results of switching trials exist to date.

We recommend clinicians to bear these potential hazards in mind while switching treatment.

In Sect. 4 we summarized benefits for the patients when switched to a certain compound and provided recommendations of appropriate switching strategies for each compound in the corresponding paragraphs.

In daily clinical practice all contributing factors have to be combined on an individual basis to choose the best switching strategy for the individual patient. This should incorporate the patient's personal preferences [195] and worries regarding the change of treatment, as well as the

Table 8 Summary of possible emerging adverse events occurring during switching of antipsychotics attributed to withdrawal and rebound syndromes or major new limitations (e.g., weight gain)

Switching to Switching from	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone	Haloperidol
Aripiprazole		Sedation, weight ↑, metab. dist.[a]	Sedation, weight ↑, metab. dist.[a]	Sedation, weight ↑, metab. dist.[a]	Prolactin ↑	Sedation, prolactin ↑	Prolactin ↑
Clozapine	Psychosis, insomnia, agitation, anxiety, cholinergic rebound		Dyskinesia, anxiety, agitation	No major TEAE reported or to be anticipated	Psychosis, dyskinesia, cholinergic rebound, RR[b] decrease, prolactin ↑	Insomnia, agitation, anxiety, cholinergic rebound	Insomnia
Olanzapine	Psychosis, insomnia, agitation, anxiety, cholinergic rebound	Weight ↑		No major TEAE reported or to be anticipated	Psychosis, cholinergic rebound, prolactin ↑	Insomnia, agitation, anxiety, cholinergic rebound	Insomnia
Quetiapine	Insomnia, agitation	Weight ↑	Weight ↑		Insomnia, prolactin ↑	Insomnia, agitation	Insomnia
Risperidone	Dyskinesia, hyperkinesia	Dyskinesia, hyperkinesia sedation, weight ↑, metab. dist.[a]	Dyskinesia, hyperkinesia, sedation, weight ↑, metab. dist.[a]	Dyskinesia, hyperkinesia sedation, weight ↑, metab. dist.[a]		Psychosis, dyskinesia, hyperkinesia	No major TEAE reported or to be anticipated
Ziprasidone	No major TEAE reported or to be anticipated	Sedation, weight ↑, metab. dist.[a]	Sedation, weight ↑, metab. dist.[a]	Sedation, weight ↑, metab. dist.[a]	Prolactin ↑		No major TEAE reported or to be anticipated
Haloperidol	Dyskinesia, hyperkinesia	Dyskinesia, hyperkinesia	Psychosis, weight ↑, dyskinesia, hyperkinesia	Psychosis, weight ↑, dyskinesia, hyperkinesia	Dyskinesia	Dyskinesia	

[a] Metabolic disturbances such as increased lipid levels or glucose disturbances

[b] Blood pressure

TEAE treatment-emergent adverse event, ↓ decrease, ↑ increase

compound's receptor binding profile, the patient's age and the concomitant medication. Additional research is warranted to analyse different switching regimens with regard to the emergence of rebound phenomena in different patient populations in order to provide better clinical advice. Further, it remains to be elucidated what factors are of importance to predict the occurrence of rebound or withdrawal syndromes. Only some factors such as PANSS scores at time of switching or duration of illness have been investigated in some switching scenarios and found to be influencing factors [80, 150].

To conclude, there is still an urgent need for further studies to explore the risk and mechanisms of discontinuation and withdrawal syndromes and how they can be avoided and treated.

Acknowledgements We thank Thelma Coutts for assistance with language. There were no sources of funding for preparation of the manuscript. The authors declare that over the past 3 years Dr. R. Musil has received research support from AstraZeneca and Janssen-Cilag, Dr. M. Riedel and Dr. K.-U. Kühn have received grants/research support from AstraZeneca and Pfizer and are speakers or on the advisory board of AstraZeneca, Pfizer, Bristol-Meyers-Squibb, Otsuka and Servier. All other authors state that they have no conflicts of interest to declare. All authors critically reviewed the final version. All authors contributed to and have approved the final manuscript; Anja Cerovecki and Richard Musil contributed equally.

References

1. Chouinard G, Chouinard VA. Atypical antipsychotics: CATIE study, drug-induced movement disorder and resulting iatrogenic psychiatric-like symptoms, supersensitivity rebound psychosis and withdrawal discontinuation syndromes. Psychother Psychosom. 2008;77(2):69–77.
2. Chouinard G, Bradwejn J, Annable L, et al. Withdrawal symptoms after long-term treatment with low-potency neuroleptics. J Clin Psychiatry. 1984;45(12):500–2.
3. Chouinard G, Jones BD, Annable L. Neuroleptic-induced supersensitivity psychosis. Am J Psychiatry. 1978;135(11): 1409–10.
4. Chouinard G, Jones BD. Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. Am J Psychiatry. 1980;137(1):16–21.
5. Chouinard G. Severe cases of neuroleptic-induced supersensitivity psychosis: diagnostic criteria for the disorder and its treatment. Schizophr Res. 1991;5(1):21–33.
6. Goudie AJ, Smith JA, Robertson A, et al. Clozapine as a drug of dependence. Psychopharmacology (Berl). 1999;142(4):369–74.
7. Borison RL. Changing antipsychotic medication: guidelines on the transition to treatment with risperidone: the Consensus Study Group on Risperidone Dosing. Clin Ther. 1996;18(4):592–607.
8. Buckley PF. Receptor-binding profiles of antipsychotics: clinical strategies when switching between agents. J Clin Psychiatry. 2007;68(Suppl. 6):5–9.
9. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. Eur Psychiatry. 2010;25(Suppl. 2):S12–21.
10. Lambert TJ. Switching antipsychotic therapy: what to expect and clinical strategies for improving therapeutic outcomes. J Clin Psychiatry. 2007;68(Suppl. 6):10–3.
11. Luchins DJ, Freed WJ, Wyatt RJ. The role of cholinergic supersensitivity in the medical symptoms associated with withdrawal of antipsychotic drugs. Am J Psychiatry. 1980; 137(11):1395–8.
12. Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. Acta Psychiatr Scand. 2006;114(1):3–13.
13. Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev. 2011; 63(1):182–217.
14. Vallone D, Picetti R, Borrelli E. Structure and function of dopamine receptors. Neurosci Biobehav Rev. 2000;24(1):125–32.
15. Andersen PH, Gingrich JA, Bates MD, et al. Dopamine receptor subtypes: beyond the D1/D2 classification. Trends Pharmacol Sci. 1990;11(6):231–6.
16. Anden NE, Carlsson A, Dahlstroem A, et al. Demonstration and mapping out of nigro-neostriatal dopamine neurons. Life Sci. 1964;3:523–30.
17. Dahlstroem A, Fuxe K. Evidence for the existence of monoamine neurons in the central nervous system: II. Experimentally induced changes in the intraneuronal amine levels of bulbospinal neuron systems. Acta Physiol Scand Suppl. 1965;Suppl. 247:1–36.
18. Glazer WM. Extrapyramidal side effects, tardive dyskinesia, and the concept of atypicality. J Clin Psychiatry. 2000;61(Suppl. 3): 16–21.
19. Reynolds GP. Antipsychotic drug mechanisms and neurotransmitter systems in schizophrenia. Acta Psychiatr Scand Suppl. 1994;380:36–40.
20. Jauss M, Krack P, Franz M, et al. Imaging of dopamine receptors with [123I]iodobenzamide single-photon emission-computed tomography in neuroleptic malignant syndrome. Mov Disord. 1996;11(6):726–8.
21. Seeman P, Weinshenker D, Quirion R, et al. Dopamine supersensitivity correlates with D2high states, implying many paths to psychosis. Proc Natl Acad Sci USA. 2005;102(9):3513–8.
22. Akhondzadeh S, Malek-Hosseini M, Ghoreishi A, et al. Effect of ritanserin, a 5HT2A/2C antagonist, on negative symptoms of schizophrenia: a double-blind randomized placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(8):1879–83.
23. Baumgarten HG, Grozdanovic Z. Psychopharmacology of central serotonergic systems. Pharmacopsychiatry. 1995;28(Suppl. 2):73–9.
24. Roth BL. Multiple serotonin receptors: clinical and experimental aspects. Ann Clin Psychiatry. 1994;6(2):67–78.
25. MacDonald GJ, Bartolome JM. A decade of progress in the discovery and development of 'atypical' antipsychotics. Prog Med Chem. 2010;49:37–80.
26. Meltzer HY, Massey BW. The role of serotonin receptors in the action of atypical antipsychotic drugs. Curr Opin Pharmacol. 2011;11(1):59–67.
27. Meltzer HY, Horiguchi M, Massey BW. The role of serotonin in the NMDA receptor antagonist models of psychosis and cognitive impairment. Psychopharmacology (Berl). 2011;213(2–3): 289–305.
28. Schmidt CJ, Sorensen SM, Kehne JH, et al. The role of 5-HT2A receptors in antipsychotic activity. Life Sci. 1995;56(25): 2209–22.
29. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and

atypical antipsychotic drugs. Neuropsychopharmacology. 2003; 28(3):519–26.
30. Freedman R, Adams CE, Leonard S. The alpha7-nicotinic acetylcholine receptor and the pathology of hippocampal interneurons in schizophrenia. J Chem Neuroanat. 2000;20(3–4): 299–306.
31. Olincy A, Harris JG, Johnson LL, et al. Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. Arch Gen Psychiatry. 2006;63(6):630–8.
32. Langmead CJ, Watson J, Reavill C. Muscarinic acetylcholine receptors as CNS drug targets. Pharmacol Ther. 2008; 117(2):232–43.
33. Raedler TJ, Bymaster FP, Tandon R, et al. Towards a muscarinic hypothesis of schizophrenia. Mol Psychiatry. 2007;12(3): 232–46.
34. Scarr E, Dean B. Muscarinic receptors: do they have a role in the pathology and treatment of schizophrenia? *J Neurochem* 2008 Dec;107(5):1188-95.
35. Fisher A, Heldman E, Gurwitz D, et al. M1 agonists for the treatment of Alzheimer's disease: novel properties and clinical update. Ann N Y Acad Sci. 1996;777:189–96.
36. Iversen SD. Behavioural evaluation of cholinergic drugs. Life Sci. 1997;60(13–14):1145–52.
37. Bymaster FP, Felder CC, Tzavara E, et al. Muscarinic mechanisms of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(7):1125–43.
38. Hein L. Adrenoceptors and signal transduction in neurons. Cell Tissue Res. 2006;326(2):541–51.
39. Marcus MM, Jardemark KE, Wadenberg ML, et al. Combined alpha2 and D2/3 receptor blockade enhances cortical glutamatergic transmission and reverses cognitive impairment in the rat. Int J Neuropsychopharmacol. 2005;8(3):315–27.
40. Svensson TH. Alpha-adrenoceptor modulation hypothesis of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(7):1145–58.
41. Ungerstedt U. Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. Acta Physiol Scand Suppl. 1971;367:69–93.
42. Muller P, Seeman P. Dopaminergic supersensitivity after neuroleptics: time-course and specificity. Psychopharmacology (Berl). 1978;60(1):1–11.
43. Ekblom B, Eriksson K, Lindstrom LH. Supersensitivity psychosis in schizophrenic patients after sudden clozapine withdrawal. Psychopharmacology (Berl). 1984;83(3):293–4.
44. Kapur S, Seeman P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: A new hypothesis. Am J Psychiatry. 2001;158(3):360–9.
45. Seeman P, Tallerico T. Rapid release of antipsychotic drugs from dopamine D2 receptors: an explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine or quetiapine. Am J Psychiatry. 1999;156(6):876–84.
46. Fallon P, Dursun SM. A naturalistic controlled study of relapsing schizophrenic patients with tardive dyskinesia and supersensitivity psychosis. J Psychopharmacol. 2011;25(6):755–62.
47. Davis KL, Rosenberg GS. Is there a limbic system equivalent of tardive dyskinesia? Biol Psychiatry. 1979;14(4):699–703.
48. Margolese HC, Chouinard G, Beauclair L, et al. Therapeutic tolerance and rebound psychosis during quetiapine maintenance monotherapy in patients with schizophrenia and schizoaffective disorder. J Clin Psychopharmacol. 2002;22(4):347–52.
49. Perenyi A, Kuncz E, Bagdy G. Early relapse after sudden withdrawal or dose reduction of clozapine. Psychopharmacology (Berl). 1985;86(1–2):244.
50. Alphs LD, Lee HS. Comparison of withdrawal of typical and atypical antipsychotic drugs: a case study. J Clin Psychiatry. 1991;52(8):346–8.
51. Parsa MA, al-Lahham YH, Ramirez LF, et al. Prolonged psychotic relapse after abrupt clozapine withdrawal. J Clin Psychopharmacol. 1993;13(2):154–5.
52. Meltzer HY. Clozapine withdrawal: serotonergic or dopaminergic mechanisms? Arch Gen Psychiatry. 1997;54(8):760–3.
53. Meltzer HY, Lee MA, Ranjan R, et al. Relapse following clozapine withdrawal: effect of neuroleptic drugs and cyproheptadine. Psychopharmacology (Berl). 1996;124(1–2):176–87.
54. Llorca PM, Penault F, Lancon C, et al. The concept of supersensitivity psychosis: the particular case of clozapine. Encephale. 1999;25(6):638–44.
55. Wadekar M, Syed S. Clozapine-withdrawal catatonia. Psychosomatics. 2010;51(4):355.
56. Ahmed S, Chengappa KN, Naidu VR, et al. Clozapine withdrawal-emergent dystonias and dyskinesias: a case series. J Clin Psychiatry. 1998;59(9):472–7.
57. Songer DA, Schulte HM. Withdrawal dyskinesia after abrupt cessation of clozapine and benztropine. J Clin Psychiatry. 1996;57(1):40.
58. Radford JM, Brown TM, Borison RL. Unexpected dystonia while changing from clozapine to risperidone. J Clin Psychopharmacol. 1995;15(3):225–6.
59. Llorca PM, Vaiva G, Lancon C. Supersensitivity psychosis in patients with schizophrenia after sudden olanzapine withdrawal. Can J Psychiatry. 2001;46(1):87–8.
60. Baldessarini RJ, Gardner DM, Garver DL. Conversions from clozapine to other antipsychotic drugs. Arch Gen Psychiatry. 1995;52(12):1071–2.
61. Lu ML, Pan JJ, Teng HW, et al. Metoclopramide-induced supersensitivity psychosis. Ann Pharmacother. 2002;36(9): 1387–90.
62. Turrone P, Remington G, Kapur S, et al. Differential effects of within-day continuous vs. transient dopamine D2 receptor occupancy in the development of vacuous chewing movements (VCMs) in rats. Neuropsychopharmacology. 2003;28(8):1433–9.
63. Turrone P, Remington G, Kapur S, et al. Continuous but not intermittent olanzapine infusion induces vacuous chewing movements in rats. Biol Psychiatry. 2005;57(4):406–11.
64. Goudie AJ, Cole JC, Sumnall HR. Olanzapine withdrawal/discontinuation-induced hyperthermia in rats. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(7):1500–3.
65. Buckley PF, Correll CU. Strategies for dosing and switching antipsychotics for optimal clinical management. J Clin Psychiatry. 2008;69(Suppl. 1):4–17.
66. Buckley PF. Introduction: the art and science of switching antipsychotic medications. J Clin Psychiatry. 2007;68(Suppl. 6):4.
67. Viguera AC, Baldessarini RJ, Hegarty JD, et al. Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. Arch Gen Psychiatry. 1997;54(1):49–55.
68. Svensson TH, Strombom U. Discontinuation of chronic clonidine treatment: evidence for facilitated brain noradrenergic neurotransmission. Naunyn Schmiedebergs Arch Pharmacol. 1977;299(1):83–7.
69. Thoolen MJ, Hendriks JC, Timmermans PB, et al. Precipitation by yohimbine of the withdrawal syndromes of clonidine, guanfacine, and methyldopa in the spontaneously hypertensive rat. J Cardiovasc Pharmacol. 1983;5(2):224–8.
70. Correll CU. Real-life switching strategies with second-generation antipsychotics. J Clin Psychiatry. 2006;67(1):160–1.
71. Edlinger M, Baumgartner S, Eltanaihi-Furtmuller N, et al. Switching between second-generation antipsychotics: why and how? CNS Drugs. 2005;19(1):27–42.
72. Lin CC, Bai YM, Wang YC, et al. Improved body weight and metabolic outcomes in overweight or obese psychiatric patients switched to amisulpride from other atypical antipsychotics. J Clin Psychopharmacol. 2009;29(6):529–36.

73. Linden M, Scheel T, Eich FX. Improvement of patient compliance after switching from conventional neuroleptics to the atypical neuroleptic amisulpride. J Psychopharmacol. 2006; 20(6):815–23.
74. Byerly MJ, Marcus RN, Tran QV, et al. Effects of aripiprazole on prolactin levels in subjects with schizophrenia during cross-titration with risperidone or olanzapine: analysis of a randomized, open-label study. Schizophr Res. 2009;107(2–3):218–22.
75. Ganguli R, Brar JS, Garbut R, et al. Changes in weight and other metabolic indicators in persons with schizophrenia following a switch to aripiprazole. Clin Schizophr Relat Psychoses. 2011; 5(2):75–9.
76. Chen CY, Lin TY, Wang CC, et al. Improvement of serum prolactin and sexual function after switching to aripiprazole from risperidone in schizophrenia: a case series. Psychiatry Clin Neurosci. 2011;65(1):95–7.
77. Kim CY, Chung S, Lee JN, et al. A 12-week, naturalistic switch study of the efficacy and tolerability of aripiprazole in stable outpatients with schizophrenia or schizoaffective disorder. Int Clin Psychopharmacol. 2009;24(4):181–8.
78. Kim SH, Ivanova O, Abbasi FA, et al. Metabolic impact of switching antipsychotic therapy to aripiprazole after weight gain: a pilot study. J Clin Psychopharmacol. 2007;27(4):365–8.
79. Lee BH, Kim YK, Park SH. Using aripiprazole to resolve antipsychotic-induced symptomatic hyperprolactinemia: a pilot study. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(4): 714–7.
80. Lin HC, Chong MY, Lee Y, et al. Switching of antipsychotics to aripiprazole in the treatment of schizophrenia. Chang Gung Med J. 2009;32(4):409–16.
81. Lu ML, Shen WW, Chen CH. Time course of the changes in antipsychotic-induced hyperprolactinemia following the switch to aripiprazole. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(8):1978–81.
82. Mir A, Shivakumar K, Williamson RJ, et al. Change in sexual dysfunction with aripiprazole: a switching or add-on study. J Psychopharmacol. 2008;22(3):244–53.
83. Pae CU, Serretti A, Chiesa A, et al. Immediate versus gradual suspension of previous treatments during switch to aripiprazole: results of a randomized, open label study. Eur Neuropsychopharmacol. 2009;19(8):562–70.
84. Pae CU, Chiesa A, Mandelli L, et al. Predictors of early worsening after switch to aripiprazole: a randomized, controlled, open-label study. Clin Drug Investig. 2010;30(3):187–93.
85. Ryckmans V, Kahn JP, Modell S, et al. Switching to aripiprazole in outpatients with schizophrenia experiencing insufficient efficacy and/or safety/tolerability issues with risperidone: a randomized, multicentre, open-label study. Pharmacopsychiatry. 2009;42(3):114–21.
86. Sarin A, Nagpal J, Bohra NK, et al. Open labeled, randomized, switch-over study of two fixed doses (10/15 mg) of aripiprazole: to evaluate its safety and efficacy in the treatment of Indian patients of schizophrenia. Indian J Psychiatry. 2004;46(1): 64–71.
87. Spurling RD, Lamberti JS, Olsen D, et al. Changes in metabolic parameters with switching to aripiprazole from another second-generation antipsychotic: a retrospective chart review. J Clin Psychiatry. 2007;68(3):406–9.
88. Stroup TS, McEvoy JP, Ring KD, et al. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). Am J Psychiatry. 2011;168(9):947–56.
89. Takeuchi H, Suzuki T, Uchida H, et al. A randomized, open-label comparison of 2 switching strategies to aripiprazole treatment in patients with schizophrenia: add-on, wait, and tapering of previous antipsychotics versus add-on and simultaneous tapering. J Clin Psychopharmacol. 2008;28(5):540–3.
90. Kim SW, Shin IS, Kim JM, et al. Effects of switching to long-acting injectable risperidone from oral atypical antipsychotics on cognitive function in patients with schizophrenia. Hum Psychopharmacol. 2009;24(7):565–73.
91. Hsu WY, Lee CI, Chiu NY, et al. Aripiprazole in treatment-refractory schizophrenia. J Psychiatr Pract. 2009;15(3):221–6.
92. Hughes D, Morcos M. Use of aripiprazole in treatment resistant schizophrenia. J Psychopharmacol. 2008;22(8):927–8.
93. Kuloglu M, Ekinci O, Albayrak Y, et al. Benefits of switching women schizophrenic patients to aripiprazole: a case study and brief review of the literature. Arch Womens Ment Health. 2010;13(5):443–7.
94. Kim SW, Shin IS, Kim JM, et al. Effectiveness of switching to aripiprazole from atypical antipsychotics in patients with schizophrenia. Clin Neuropharmacol. 2009;32(5):243–9.
95. Mago R. Proposed strategies for successful clinical management with aripiprazole. Expert Opin Pharmacother. 2008;9(8):1279–90.
96. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther. 2002;302(1):381–9.
97. Schering-Plough Corporation. Saphris (Asenapine) sublingual tablets: US prescribing information. http://www.spfiles.com/pisaphrisv1.pdf (Accessed 2 Feb 2012).
98. Kane JM, Mackle M, Snow-Adami L, et al. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. J Clin Psychiatry. 2011;72(3):349–55.
99. Schoemaker J, Naber D, Vrijland P, et al. Long-term assessment of asenapine vs. olanzapine in patients with schizophrenia or schizoaffective disorder. Pharmacopsychiatry. 2010;43(4):138–46.
100. Buchanan RW, Panagides J, Zhao J, et al. Asenapine versus olanzapine in people with persistent negative symptoms of schizophrenia. J Clin Psychopharmacol. 2012;32(1):36–45.
101. Kane JM, Cohen M, Zhao J, et al. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. J Clin Psychopharmacol. 2010;30(2):106–15.
102. Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. J Clin Psychiatry. 2007;68(10):1492–500.
103. Dubovsky SL, Frobose C, Phiri P, et al. Short-term safety and pharmacokinetic profile of asenapine in older patients with psychosis. Int J Geriatr Psychiatry. 2012;27(5):472–82.
104. Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. Int J Clin Pract. 2009;63(12):1762–84.
105. Kane JM, Lauriello J, Laska E, et al. Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. J Clin Psychopharmacol. 2008;28 Suppl. 1(2):S29–35.
106. Potkin SG, Litman RE, Torres R, et al. Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. J Clin Psychopharmacol. 2008;28 Suppl. 1(2):S4–11.
107. Cutler AJ, Kalali AH, Weiden PJ, et al. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. J Clin Psychopharmacol. 2008;28(2 Suppl. 1):S20–8.
108. Vanda Pharmaceuticals. Fanapt (iloperidone) tablets. http://www.pharma.us.novartis.com/product/pi/pdf/fanapt.pdf (Accessed 6 Feb 2012).
109. Weiden PJ, Cutler AJ, Polymeropoulos MH, et al. Safety profile of iloperidone: a pooled analysis of 6-week acute-phase pivotal trials. J Clin Psychopharmacol. 2008;28 Suppl. 1(2):S12–9.

110. Kalkman HO, Subramanian N, Hoyer D. Extended radioligand binding profile of iloperidone: a broad spectrum dopamine/serotonin/norepinephrine receptor antagonist for the management of psychotic disorders. Neuropsychopharmacology. 2001;25(6):904–14.
111. Citrome L. Lurasidone for schizophrenia: a review of the efficacy and safety profile for this newly approved second-generation antipsychotic. Int J Clin Pract. 2011;65(2):189–210.
112. Sunovion. Latuda (lurasidone HCl) tablets: prescribing information. Available from URL: http://www.latuda.com/LatudaPrescribingInformation.pdf (Accessed 9 Feb 2012).
113. Nakamura M, Ogasa M, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. J Clin Psychiatry. 2009;70(6):829–36.
114. Cucchiaro J, Potkin SG, Ogasa M, et al. A double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. Schizophr Bull. 2009;35(Suppl. 1):342–3.
115. Potkin SG, Ogasa M, Cucchiaro J, Loebel A. Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. Schizophr Res. 2011;132(2–3):101–7.
116. Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. Am J Psychiatry. 2011;168(9):957–67.
117. Costa e Silva JA, Alvarez N, Mazzotti G, et al. Olanzapine as alternative therapy for patients with haloperidol-induced extrapyramidal symptoms: results of a multicenter, collaborative trial in Latin America. J Clin Psychopharmacol. 2001;21(4):375–81.
118. Dossenbach MR, Kratky P, Schneidman M, et al. Evidence for the effectiveness of olanzapine among patients nonresponsive and/or intolerant to risperidone. J Clin Psychiatry. 2001;62(Suppl 2):28–34.
119. Dossenbach MRK, Beuzen JN, Avnon M, et al. The effectiveness of olanzapine in treatment-refractory schizophrenia when patients are nonresponsive to or unable to tolerate clozapine. Clin Ther. 2000;22(9):1021–34.
120. Faries DE, Ascher-Svanum H, Nyhuis AW, Kinon BJ. Switching from risperidone to olanzapine in a one-year, randomized, open-label effectiveness study of schizophrenia. Curr Med Res Opin. 2008;24(5):1399–405.
121. Godleski LS, Goldsmith LJ, Vieweg WV, Zettwoch NC, Stikovac DM, Lewis SJ. Switching from depot antipsychotic drugs to olanzapine in patients with chronic schizophrenia. J Clin Psychiatry. 2003;64(2):119–22.
122. Henderson DC, Nasrallah RA, Goff DC. Switching from clozapine to olanzapine in treatment-refractory schizophrenia: safety, clinical efficacy, and predictors of response. J Clin Psychiatry. 1998;59(11):585–8.
123. Lee CT, Conde BJ, Mazlan M, et al. Switching to olanzapine from previous antipsychotics: a regional collaborative multicenter trial assessing 2 switching techniques in Asia Pacific. J Clin Psychiatry. 2002;63(7):569–76.
124. Lindenmayer JP, Czobor P, Volavka J, et al. Olanzapine in refractory schizophrenia after failure of typical or atypical antipsychotic treatment: an open-label switch study. J Clin Psychiatry. 2002;63(10):931–5.
125. Kim KS, Pae CU, Chae JH, et al. Effects of olanzapine on prolactin levels of female patients with schizophrenia treated with risperidone. J Clin Psychiatry. 2002;63(5):408–13.
126. Kinon BJ, Basson BR, Gilmore JA, Malcolm S, Stauffer VL. Strategies for switching from conventional antipsychotic drugs or risperidone to olanzapine. J Clin Psychiatry. 2000;61(11):833–40.
127. Kluge M, Wehmeier PM, Dittmann RW, et al. A simple switching strategy for inadequately treated patients with schizophrenia to olanzapine: changes in psychopathology and subjective well-being. Pharmacopsychiatry. 2005;38(1):6–12.
128. Labelle A, Bourget D, Boulay LJ, Ellis J, Tessier P. Switching outpatients with schizophrenia and related disorders on long-acting injectable antipsychotics to olanzapine: an open-label naturalistic pilot study. J Clin Psychopharmacol. 2002;22(6):545–53.
129. Lu Z, Hu J, Chen CK, et al. Effectiveness and safety of olanzapine in the treatment of schizophrenia among Asian patients switching from conventional antipsychotics. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(1):32–40.
130. Novick D, Haro JM, Suarez D, Marques-Teixeira J, Naber D. Clinical consequences of switching antipsychotic drugs in outpatients with schizophrenia: 36-month results from the European Schizophrenia Outpatient Health Outcomes study. Int Clin Psychopharmacol. 2008;23(4):203–8.
131. Ritchie CW, Chiu E, Harrigan S, et al. The impact upon extrapyramidal side effects, clinical symptoms and quality of life of a switch from conventional to atypical antipsychotics (risperidone or olanzapine) in elderly patients with schizophrenia. Int J Geriatr Psychiatry. 2003;18(5):432–40.
132. Takahashi H, Kamata M, Yoshida K, Ishigooka J, Higuchi H. Switching to olanzapine after unsuccessful treatment with risperidone during the first episode of schizophrenia: an open-label trial. J Clin Psychiatry. 2006;67(10):1577–82.
133. Littrell KH, Johnson CG, Hilligoss NM, Peabody CD, Littrell SH. Switching clozapine responders to olanzapine. J Clin Psychiatry. 2000;61(12):912–5.
134. Delassus-Guenault N, Jegouzo A, Odou P, et al. Clozapine-olanzapine: a potentially dangerous switch: a report of two cases. J Clin Pharm Ther. 1999;24(3):191–5.
135. Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M, Hough D. A 52-week open-label study of the safety and tolerability of paliperidone palmitate in patients with schizophrenia. J Psychopharmacol. 2011;25(5):685–97.
136. Hough D, Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr Res. 2010;116(2–3):107–17.
137. Kramer M, Litman R, Hough D, et al. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. Int J Neuropsychopharmacol. 2010;13(5):635–47.
138. Janssen Pharmaceuticals Inc. InvegaSustenna (paliperidone palmitate) Extended-release injectable suspension for intramuscular use. http://www.invegasustenna.com/important-product-information (Accessed 2 Oct 2012).
139. Hoy SM, Scott LJ, Keating GM. Intramuscular paliperidone palmitate. CNS Drugs. 2010;24(3):227–44.
140. Nasrallah HA, Gopal S, Gassmann-Mayer C, et al. A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia. Neuropsychopharmacology. 2010;35(10):2072–82.
141. Johnson & Johnson Pharmaceutical Research & Development L.L.C. Efficacy and safety of a long acting anti-psychotic versus placebo inpatients with schizophrenia. http://download.veritasmedicine.com/PDF/CR003562_CSR.pdf (Accessed 2 Oct 2012).
142. Gopal S, Gassmann-Mayer C, Palumbo J, Samtani MN, Shiwach R, Alphs L. Practical guidance for dosing and switching paliperidone palmitate treatment in patients with schizophrenia. Curr Med Res Opin. 2010;26(2):377–87.

143. Samtani MN, Gopal S, Gassmann-Mayer C, Alphs L, Palumbo JM. Dosing and switching strategies for paliperidone palmitate: based on population pharmacokinetic modelling and clinical trial data. CNS Drugs. 2011;25(10):829–45.
144. Janssen Pharmaceuticals. INVEGA SUSTENNA (paliperidone palmitate) Extended-Release Injectable Suspension for intramuscular use. Available from URL: http://www.invegasustenna.com/important-product-information (Accessed 5 May 2012).
145. Lai CH. Improvement of oral dyskinesia after switching from aripiprazole to paliperidone: a case report. J Neuropsychiatry Clin Neurosci. 2011;23(3):E18.
146. Teng PR, Lane HY. Emergence of neuroleptic malignant syndrome while switching between risperidone and paliperidone. J Neuropsychiatry Clin Neurosci. 2011;23(4):E16–7.
147. Cortese L, Caligiuri MP, Williams R, et al. Reduction in neuroleptic-induced movement disorders after a switch to quetiapine in patients with schizophrenia. J Clin Psychopharmacol. 2008;28(1):69–73.
148. Gupta S, Masand PS, Virk S, et al. Weight decline in patients switching from olanzapine to quetiapine. Schizophr Res. 2004;70(1):57–62.
149. Larmo I, De Nayer A, Windhager E et al. Efficacy and tolerability of quetiapine in patients with schizophrenia who switched from haloperidol, olanzapine or risperidone. Hum Psychopharmacol. 2005;20(8):573–81.
150. Nakajima M, Terao T, Iwata N, Nakamura J. Switching female schizophrenic patients to quetiapine from conventional antipsychotic drugs: effects on hyperprolactinemia. Pharmacopsychiatry. 2005;38(1):17–9.
151. Ganesan S, Agambaram V, Randeree F, Eggens I, Huizar K, Meulien D. Switching from other antipsychotics to once-daily extended release quetiapine fumarate in patients with schizophrenia. Curr Med Res Opin. 2008;24(1):21–32.
152. Moller HJ, Johnson S, Mateva T, et al. Evaluation of the feasibility of switching from immediate release quetiapine to extended release quetiapine fumarate in stable outpatients with schizophrenia. Int Clin Psychopharmacol. 2008;23(2):95–105.
153. Ganguli R, Brar JS, Mahmoud R, Berry SA, Pandina GJ. Assessment of strategies for switching patients from olanzapine to risperidone: a randomized, open-label, rater-blinded study. BMC Med. 2008;6:17.
154. Still DJ, Dorson PG, Crismon ML, Pousson C. Effects of switching inpatients with treatment-resistant schizophrenia from clozapine to risperidone. Psychiatr Serv. 1996;47(12):1382–4.
155. Kirov GK, Murray RM, Seth RV, Feeney S. Observations on switching patients with schizophrenia to risperidone treatment. Risperidone Switching Study Group. Acta Psychiatr Scand. 1997;95(5):439–43.
156. Malla AK, Norman RM, Kotteda V, Zirul S. Switching from therapy with typical antipsychotic agents to risperidone: long-term impact on patient outcome. Clin Ther. 1999;21(5):806–17.
157. Meyer JM, Pandina G, Bossie CA, Turkoz I, Greenspan A. Effects of switching from olanzapine to risperidone on the prevalence of the metabolic syndrome in overweight or obese patients with schizophrenia or schizoaffective disorder: analysis of a multicenter, rater-blinded, open-label study. Clin Ther. 2005;27(12):1930–41.
158. Nakanishi S, Kunugi H, Murray RM, Nojima S, Ogawa T, Takahashi T. Effects of switching from conventional antipsychotics to risperidone in Japanese patients with chronic schizophrenia. Psychiatry Clin Neurosci. 2006;60(6):751–7.
159. van Os J, Bossie CA, Lasser RA. Improvements in stable patients with psychotic disorders switched from oral conventional antipsychotics therapy to long-acting risperidone. Int Clin Psychopharmacol. 2004;19(4):229–32.
160. Mahmoud RA, Engelhart LM, Janagap CC, Oster G, Ollendorf D. Risperidone versus conventional antipsychotics for schizophrenia and schizoaffective disorder: symptoms, quality of life and resource use under customary clinical care. Clin Drug Investig. 2004;24(5):275–86.
161. Hawley C, Turner M, Latif MA, Curtis V, Saleem PT, Wilton K. Switching stable patients with schizophrenia from depot and oral antipsychotics to long-acting injectable risperidone: reasons for switching and safety. Hum Psychopharmacol. 2010;25(1):37–46.
162. Marinis TD, Saleem PT, Glue P, et al. Switching to long-acting injectable risperidone is beneficial with regard to clinical outcomes, regardless of previous conventional medication in patients with schizophrenia. Pharmacopsychiatry. 2007;40(6):257–63.
163. Muscatello MR, Bruno A, Pandolfo G, Mico U, Settineri S, Zoccali R. Emerging treatments in the management of schizophrenia: focus on sertindole. Drug Des Devel Ther. 2010;4:187–201.
164. de Hert M, Mittoux A, He Y, Peuskens J. Metabolic parameters in the short- and long-term treatment of schizophrenia with sertindole or risperidone. Eur Arch Psychiatry Clin Neurosci. 2011;261(4):231–9.
165. Berecz R, Glaub T, Kellermann M, de la Rubia A, Llerena A, Degrell I. Clozapine withdrawal symptoms after change to sertindole in a schizophrenic patient. Pharmacopsychiatry. 2000;33(1):42–4.
166. Hanisch F, Friedemann J, Pillmann F. Combined treatment with quetiapine and sertindole in therapy refractory insomnia after clozapine discontinuation. J Psychopharmacol. 2010;24(11):1725–6.
167. Perquin LN. Treatment with the new antipsychotic sertindole for late-occurring undesirable movement effects. Int Clin Psychopharmacol. 2005;20(6):335–8.
168. Thomas SH, Drici MD, Hall GC, et al. Safety of sertindole versus risperidone in schizophrenia: principal results of the sertindole cohort prospective study (SCoP). Acta Psychiatr Scand. 2010;122(5):345–55.
169. Alptekin K, Hafez J, Brook S, et al. Efficacy and tolerability of switching to ziprasidone from olanzapine, risperidone or haloperidol: an international, multicenter study. Int Clin Psychopharmacol. 2009;24(5):229–38.
170. Harvey PD, Meltzer H, Simpson GM, et al. Improvement in cognitive function following a switch to ziprasidone from conventional antipsychotics, olanzapine, or risperidone in outpatients with schizophrenia. Schizophr Res. 2004;66(2–3):101–13.
171. Karayal ON, Glue P, Bachinsky M, et al. Switching from quetiapine to ziprasidone: a sixteen-week, open-label, multicenter study evaluating the effectiveness and safety of ziprasidone in outpatient subjects with schizophrenia or schizoaffective disorder. J Psychiatr Pract. 2011;17(2):100–9.
172. Weiden PJ, Daniel DG, Simpson G, Romano SJ. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. J Clin Psychopharmacol. 2003;23(6):595–600.
173. Kim SW, Shin IS, Kim JM, Bae KY, Yang SJ, Yoon JS. Effectiveness of switching from aripiprazole to ziprasidone in patients with schizophrenia. Clin Neuropharmacol. 2010;33(3):121–5.
174. Montes JM, Rodriguez JL, Balbo E, et al. Improvement in antipsychotic-related metabolic disturbances in patients with schizophrenia switched to ziprasidone. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(2):383–8.
175. Rossi A, Vita A, Tiradritti P, Romeo F. Assessment of clinical and metabolic status, and subjective well-being, in schizophrenic patients switched from typical and atypical

antipsychotics to ziprasidone. Int Clin Psychopharmacol. 2008;23(4):216–22.
176. Stip E, Zhornitsky S, Potvin S, Tourjman V. Switching from conventional antipsychotics to ziprasidone: a randomized, open-label comparison of regimen strategies. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(6):997–1000.
177. Weiden PJ, Simpson GM, Potkin SG, O'Sullivan RL. Effectiveness of switching to ziprasidone for stable but symptomatic outpatients with schizophrenia. J Clin Psychiatry. 2003;64(5): 580–8.
178. Rossi A, Canas F, Fagiolini A, et al. Switching among antipsychotics in everyday clinical practice: focus on ziprasidone. Postgrad Med. 2011;123(1):135–59.
179. Essock SM, Covell NH, Davis SM, Stroup TS, Rosenheck RA, Lieberman JA. Effectiveness of switching antipsychotic medications. Am J Psychiatry. 2006;163(12):2090–5.
180. Faries DE, Ascher-Svanum H, Nyhuis AW, Kinon BJ. Clinical and economic ramifications of switching antipsychotics in the treatment of schizophrenia. BMC Psychiatry. 2009;9:54.
181. Rosenheck RA, Davis S, Covell N, et al. Does switching to a new antipsychotic improve outcomes? Data from the CATIE trial. Schizophr Res. 2009;107(1):22–9.
182. Miller CH, Hummer M, Oberbauer H, Kurzthaler I, DeCol C, Fleischhacker WW. Risk factors for the development of neuroleptic induced akathisia. Eur Neuropsychopharmacol. 1997;7(1): 51–5.
183. Haddad PM, Das A, Keyhani S, Chaudhry IB. Antipsychotic drugs and extrapyramidal side effects in first episode psychosis: a systematic review of head-head comparisons. J Psychopharmacol. 2012;26(5 Suppl):15–26.
184. Stubner S, Rustenbeck E, Grohmann R, et al. Severe and uncommon involuntary movement disorders due to psychotropic drugs. Pharmacopsychiatry. 2004;37(Suppl 1):S54–64.
185. Burns T, Chabannes JP, Demyttenaere K. Switching antipsychotic medications: general recommendations and switching to amisulpride. Curr Med Res Opin. 2002;18(4):201–8.
186. Conley RR, Kelly DL. Drug-drug interactions associated with second-generation antipsychotics: considerations for clinicians and patients. Psychopharmacol Bull. 2007;40(1):77–97.
187. de Leon J, Santoro V, D'Arrigo C, Spina E. Interactions between antiepileptics and second-generation antipsychotics. Expert Opin Drug Metab Toxicol. 2012;8(3):311–34.
188. Urichuk L, Prior TI, Dursun S, Baker G. Metabolism of atypical antipsychotics: involvement of cytochrome p450 enzymes and relevance for drug-drug interactions. Curr Drug Metab. 2008;9(5):410–8.
189. Mori K, Nagao M, Yamashita H, Morinobu S, Yamawaki S. Effect of switching to atypical antipsychotics on memory in patients with chronic schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28(4):659–65.
190. Davis JM, Leucht S. Commentary on strategies for switching antipsychotics. BMC Med. 2008;6:18.
191. Kane JM, Leucht S, Carpenter D, Docherty JP. The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders: introduction: methods, commentary, and summary. J Clin Psychiatry. 2003;64(Suppl 12):5–19.
192. Edlinger M, Wolfgang FW. Review: no evidence to support gradual over abrupt switching of antipsychotics. Evid Based Ment Health. 2006;9(1):10.
193. Remington G, Chue P, Stip E, Kopala L, Girard T, Christensen B. The crossover approach to switching antipsychotics: what is the evidence? Schizophr Res. 2005;76(2–3):267–72.
194. Miodownik C, Lerner V, Kibari A, Toder D, Cohen H. The effect of sudden clozapine discontinuation on management of schizophrenic patients: A retrospective controlled study. J Clin Psychiatry. 2006;67(8):1204–8.
195. Scheifler PL, Weiden PJ. Beyond psychopharmacology. Psychosocial strategies for getting the best results when switching antipsychotic medications. Postgrad Med. 2006;Spec No: 45–53.
196. Abbas AI, Hedlund PB, Huang XP, Tran TB, Meltzer HY, Roth BL. Amisulpride is a potent 5-HT7 antagonist: relevance for antidepressant actions in vivo. Psychopharmacology (Berl). 2009;205(1):119–28.
197. Keck PE Jr, McElroy SL. Aripiprazole: a partial dopamine D2 receptor agonist antipsychotic. Expert Opin Investig Drugs. 2003;12(4):655–62.
198. Shahid M, Walker GB, Zorn SH, Wong EH. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. J Psychopharmacol. 2009;23(1):65–73.
199. Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology. 1996;14(2):87–96.
200. Citrome L. Iloperidone: chemistry, pharmacodynamics, pharmacokinetics and metabolism, clinical efficacy, safety and tolerability, regulatory affairs, and an opinion. Expert Opin Drug Metab Toxicol. 2010;6(12):1551–64.
201. Leysen JE, Janssen PM, Megens AA, Schotte A. Risperidone: a novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharmacologic activity. J Clin Psychiatry. 1994;55(Suppl):5–12.
202. Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. Neuropsychopharmacology. 1998;18(2):63–101.
203. Ishibashi T, Horisawa T, Tokuda K, et al. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. J Pharmacol Exp Ther. 2010;334(1):171–81.
204. Bishara D, Taylor D. Upcoming agents for the treatment of schizophrenia: mechanism of action, efficacy and tolerability. Drugs. 2008;68(16):2269–92.
205. Balle T, Perregaard J, Ramirez MT, et al. Synthesis and structure-affinity relationship investigations of 5-heteroaryl-substituted analogues of the antipsychotic sertindole. A new class of highly selective alpha(1) adrenoceptor antagonists. J Med Chem. 2003;46(2):265–83.
206. Seeger TF, Seymour PA, Schmidt AW, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther. 1995;275(1):101–13.
207. Kongsamut S, Roehr JE, Cai J, et al. Iloperidone binding to human and rat dopamine and 5-HT receptors. Eur J Pharmacol. 1996;317(2–3):417–23.
208. Meyer JM, Loebel AD, Schweizer E. Lurasidone: a new drug in development for schizophrenia. Expert Opin Investig Drugs. 2009;18(11):1715–26.
209. Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors focus on newer generation compounds. Life Sci. 2000;68(1):29–39.
210. Mork A, Witten LM, Arnt J. Effect of sertindole on extracellular dopamine, acetylcholine, and glutamate in the medial prefrontal cortex of conscious rats: a comparison with risperidone and exploration of mechanisms involved. Psychopharmacology (Berl). 2009;206(1):39–49.
211. Knight JA, Smith C, Toohey N, Klein MT, Teitler M. Pharmacological analysis of the novel, rapid, and potent inactivation of the human 5-hydroxytryptamine7 receptor by risperidone, 9-OH-risperidone, and other inactivating antagonists. Mol Pharmacol. 2009;75(2):374–80.
212. Subramanian N, Kalkman HO. Receptor profile of P88–8991 and P95–12113, metabolites of the novel antipsychotic iloperidone. Prog Neuropsychopharmacol Biol Psychiatry. 2002;26(3): 553–60.

213. Schotte A, Janssen PF, Gommeren W, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology (Berl). 1996; 124(1–2):57–73.
214. Kalkman HO, Feuerbach D, Lotscher E, Schoeffter P. Functional characterization of the novel antipsychotic iloperidone at human D2, D3, alpha 2C, 5-HT6, and 5-HT1A receptors. Life Sci. 2003;73(9):1151–9.
215. Cosi C, Koek W. Agonist, antagonist, and inverse agonist properties of antipsychotics at human recombinant 5-HT(1A) receptors expressed in HeLa cells. Eur J Pharmacol. 2001;433(1):55–62.
216. Herrick-Davis K, Grinde E, Teitler M. Inverse agonist activity of atypical antipsychotic drugs at human 5-hydroxytryptamine2C receptors. J Pharmacol Exp Ther. 2000;295(1):226–32.
217. Zahrt J, Taylor JR, Mathew RG, Arnsten AF. Supranormal stimulation of D1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory performance. J Neurosci. 1997;17(21):8528–35.
218. Granon S, Passetti F, Thomas KL, Dalley JW, Everitt BJ, Robbins TW. Enhanced and impaired attentional performance after infusion of D1 dopaminergic receptor agents into rat prefrontal cortex. J Neurosci. 2000;20(3):1208–15.
219. Mattay VS, Goldberg TE, Fera F, et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci USA. 2003;100(10):6186–91.
220. Xu TX, Sotnikova TD, Liang C, et al. Hyperdopaminergic tone erodes prefrontal long-term potential via a D2 receptor-operated protein phosphatase gate. J Neurosci. 2009;29(45):14086–99.
221. Tarsy D, Baldessarini RJ. Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics? Mov Disord. 2006;21(5):589–98.
222. Joseph JD, Wang YM, Miles PR, et al. Dopamine autoreceptor regulation of release and uptake in mouse brain slices in the absence of D(3) receptors. Neuroscience. 2002;112(1):39–49.
223. De Mei C, Ramos M, Iitaka C, Borrelli E. Getting specialized: presynaptic and postsynaptic dopamine D2 receptors. Curr Opin Pharmacol. 2009;9(1):53–8.
224. Rondou P, Haegeman G, Van CK. The dopamine D4 receptor: biochemical and signalling properties. Cell Mol Life Sci. 2010;67(12):1971–86.
225. Meador-Woodruff JH, Grandy DK, Van Tol HH, et al. Dopamine receptor gene expression in the human medial temporal lobe. Neuropsychopharmacology. 1994;10(4):239–48.
226. Wong AH, Van Tol HH. The dopamine D4 receptors and mechanisms of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(7):1091–9.
227. Wilson JM, Sanyal S, Van Tol HH. Dopamine D2 and D4 receptor ligands: relation to antipsychotic action. Eur J Pharmacol. 1998;351(3):273–86.
228. Pucadyil TJ, Kalipatnapu S, Chattopadhyay A. The serotonin1A receptor: a representative member of the serotonin receptor family. Cell Mol Neurobiol. 2005;25(3–4):553–80.
229. Luna-Munguia H, Manuel-Apolinar L, Rocha L, Meneses A. 5-HT1A receptor expression during memory formation. Psychopharmacology (Berl). 2005;181(2):309–18.
230. Kusserow H, Davies B, Hortnagl H, et al. Reduced anxiety-related behaviour in transgenic mice overexpressing serotonin 1A receptors. Brain Res Mol Brain Res. 2004;129(1–2):104–16.
231. Meltzer HY, Sumiyoshi T. Does stimulation of 5-HT(1A) receptors improve cognition in schizophrenia? Behav Brain Res. 2008;195(1):98–102.
232. Sumiyoshi T, Park S, Jayathilake K, Roy A, Ertugrul A, Meltzer HY. Effect of buspirone, a serotonin1A partial agonist, on cognitive function in schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr Res. 2007;95(1–3):158–68.
233. Sumiyoshi T, Meltzer HY. Serotonin 1A receptors in memory function. Am J Psychiatry. 2004;161(8):1505–6.
234. Ohno Y. Therapeutic role of 5-HT1A receptors in the treatment of schizophrenia and Parkinson's disease. CNS Neurosci Ther. 2011;17(1):58–65.
235. Neal-Beliveau BS, Joyce JN, Lucki I. Serotonergic involvement in haloperidol-induced catalepsy. J Pharmacol Exp Ther. 1993;265(1):207–17.
236. Prinssen EP, Colpaert FC, Koek W. 5-HT1A receptor activation and anti-cataleptic effects: high-efficacy agonists maximally inhibit haloperidol-induced catalepsy. Eur J Pharmacol. 2002;453(2–3):217–21.
237. Prinssen EP, Koek W, Colpaert FC, Kleven MS. Repeated treatment with 8-OH-DPAT induces tolerance to its ability to produce the 5-HT1A behavioural syndrome, but not to its ability to attenuate haloperidol-induced catalepsy. Behav Pharmacol. 2000;11(3–4):299–305.
238. Shimizu S, Tatara A, Imaki J, Ohno Y. Role of cortical and striatal 5-HT1A receptors in alleviating antipsychotic-induced extrapyramidal disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(6):877–81.
239. Ohno Y, Shimizu S, Imaki J. Effects of tandospirone, a 5-HT1A agonistic anxiolytic agent, on haloperidol-induced catalepsy and forebrain Fos expression in mice. J Pharmacol Sci. 2009; 109(4):593–9.
240. Ohno Y, Shimizu S, Imaki J, et al. Anticataleptic 8-OH-DPAT preferentially counteracts with haloperidol-induced Fos expression in the dorsolateral striatum and the core region of the nucleus accumbens. Neuropharmacology. 2008;55(5):717–23.
241. Ohno Y, Shimizu S, Imaki J, et al. Evaluation of the antibradykinetic actions of 5-HT1A agonists using the mouse pole test. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(5): 1302–7.
242. Navailles S, De Deurwaerdère P. Presynaptic control of serotonin on striatal dopamine function. Psychopharmacology (Berl). 2011;213(2–3):213–42.
243. Meltzer HY, Li Z, Kaneda Y, Ichikawa J. Serotonin receptors: their key role in drugs to treat schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(7):1159–72.
244. Remington G, Kapur S. D2 and 5-HT2 receptor effects of antipsychotics: bridging basic and clinical findings using PET. J Clin Psychiatry. 1999;60(Suppl 10):15–9.
245. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry. 1996;153(4): 466–76.
246. Horacek J, Bubenikova-Valesova V, Kopecek M, et al. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. CNS Drugs. 2006;20(5):389–409.
247. Meltzer HY, Huang M. In vivo actions of atypical antipsychotic drug on serotonergic and dopaminergic systems. Prog Brain Res. 2008;172:177–97.
248. Creed-Carson M, Oraha A, Nobrega JN. Effects of 5-HT(2A) and 5-HT(2C) receptor antagonists on acute and chronic dyskinetic effects induced by haloperidol in rats. Behav Brain Res. 2011;219(2):273–9.
249. Codony X, Vela JM, Ramirez MJ. 5-HT(6) receptor and cognition. Curr Opin Pharmacol. 2011;11(1):94–100.
250. Marazziti D, Baroni S, Dell'Osso MC, Bordi F, Borsini F. Serotonin receptors of type 6 (5-HT6): what can we expect from them? Curr Med Chem. 2011;18(18):2783–90.
251. Hedlund PB. The 5-HT7 receptor and disorders of the nervous system: an overview. Psychopharmacology (Berl). 2009;206(3): 345–54.

252. Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. Prog Neurobiol. 2001;63(6):637–72.
253. Fukagawa K, Sakata T, Shiraishi T, et al. Neuronal histamine modulates feeding behavior through H1-receptor in rat hypothalamus. Am J Physiol. 1989;256(3 Pt 2):R605–11.
254. Yanai K, Son LZ, Endou M, et al. Behavioural characterization and amounts of brain monoamines and their metabolites in mice lacking histamine H1 receptors. Neuroscience. 1998;87(2): 479–87.
255. Schwartz JC, Arrang JM, Garbarg M, Traiffort E. Histamine. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press; 1995. p. 397–405.
256. Haas H, Panula P. The role of histamine and the tuberomamillary nucleus in the nervous system. Nat Rev Neurosci. 2003;4(2):121–30.
257. Mercer LP, Kelley DS, Humphries LL, Dunn JD. Manipulation of central nervous system histamine or histaminergic receptors (H1) affects food intake in rats. J Nutr. 1994;124(7):1029–36.
258. Watanabe T, Yanai K. Studies on functional roles of the histaminergic neuron system by using pharmacological agents, knockout mice and positron emission tomography. Tohoku J Exp Med. 2001;195(4):197–217.
259. Masaki T, Yoshimatsu H, Chiba S, Watanabe T, Sakata T. Targeted disruption of histamine H1-receptor attenuates regulatory effects of leptin on feeding, adiposity, and UCP family in mice. Diabetes. 2001;50(2):385–91.
260. Schwartz JC, Arrang JM, Garbarg M, Pollard H, Ruat M. Histaminergic transmission in the mammalian brain. Physiol Rev. 1991;71:1–51.
261. Bhargava KP, Kulshrestha VK, Santhakumari G, Srivastava YP. Mechanism of histamine-induced antidiuretic response. Br J Pharmacol. 1973;47(4):700–6.
262. Kjaer A, Knigge U, Rouleau A, Garbarg M, Warberg J. Dehydration-induced release of vasopressin involves activation of hypothalamic histaminergic neurons. Endocrinology. 1994; 135(2):675–81.
263. Poulakos JJ, Gertner SB. Studies on the cardiovascular actions of central histamine H1 and H2 receptors. J Pharmacol Exp Ther. 1989;250(2):500–7.
264. Malmberg-Aiello P, Lamberti C, Ghelardini C, Giotti A, Bartolini A. Role of histamine in rodent antinociception. Br J Pharmacol. 1994;111(4):1269–79.
265. Malmberg-Aiello P, Lamberti C, Ipponi A, Hanninen J, Ghelardini C, Bartolini A. Effects of two histamine-N-methyltransferase inhibitors, SKF 91488 and BW 301 U, in rodent antinociception. Naunyn Schmiedebergs Arch Pharmacol. 1997;355(3):354–60.
266. Traiffort E, Pollard H, Moreau J, et al. Pharmacological characterization and autoradiographic localization of histamine H2 receptors in human brain identified with [125I]iodoaminopotentidine. J Neurochem. 1992;59(1):290–9.
267. Vizuete ML, Traiffort E, Bouthenet ML, et al. Detailed mapping of the histamine H2 receptor and its gene transcripts in guinea-pig brain. Neuroscience. 1997;80(2):321–43.
268. Privou C, Knoche A, Hasenohrl RU, Huston JP. The H1- and H2-histamine blockers chlorpheniramine and ranitidine applied to the nucleus basalis magnocellularis region modulate anxiety and reinforcement related processes. Neuropharmacology. 1998;37(8):1019–32.
269. Dhawan BN, Shukla R, Srimal RC. Analysis of histamine receptors in the central thermoregulatory mechanism of *Mastomys natalensis*. Br J Pharmacol. 1982;75(1):145–9.
270. Donoso AO, Bannza AM. Acute effects of histamine on plasma prolactin and luteininzing hormone levels in male rats. J Neural Transm. 1976;39(1–2):95–101.
271. Appl H, Holzammer T, Dove S, Haen E, Strasser A, Seifert R. Interactions of recombinant human histamine H(1), H (2), H (3), and H (4) receptors with 34 antidepressants and antipsychotics. Naunyn Schmiedebergs Arch Pharmacol. 2012;385(2):145–70.
272. Arrang JM, Garbarg M, Schwartz JC. Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. Nature. 1983;302(5911):832–7.
273. Ookuma K, Sakata T, Fukagawa K, et al. Neuronal histamine in the hypothalamus suppresses food intake in rats. Brain Res. 1993;628(1–2):235–42.
274. Schwartz JC, Arrang JM, Garbarg M, Korner M. Properties and roles of the three subclasses of histamine receptors in brain. J Exp Biol. 1986;124:203–24.
275. Haaksma EE, Leurs R, Timmerman H. Histamine receptors: subclasses and specific ligands. Pharmacol Ther. 1990;47(1): 73–104.
276. Brown RE, Reymann KG. Histamine H3 receptor-mediated depression of synaptic transmission in the dentate gyrus of the rat in vitro. J Physiol. 1996;496(Pt 1):175–84.
277. Garcia M, Floran B, Arias-Montano JA, Young JM, Aceves J. Histamine H3 receptor activation selectively inhibits dopamine D1 receptor-dependent [3H]GABA release from depolarization-stimulated slices of rat substantia nigra pars reticulata. Neuroscience. 1997;80(1):241–9.
278. Schlicker E, Fink K, Hinterthaner M, Gothert M. Inhibition of noradrenaline release in the rat brain cortex via presynaptic H3 receptors. Naunyn Schmiedebergs Arch Pharmacol. 1989;340(6): 633–8.
279. Schlicker E, Fink K, Detzner M, Gothert M. Histamine inhibits dopamine release in the mouse striatum via presynaptic H3 receptors. J Neural Transm Gen Sect. 1993;93(1):1–10.
280. Arrang JM, Drutel G, Schwartz JC. Characterization of histamine H3 receptors regulating acetylcholine release in rat entorhinal cortex. Br J Pharmacol. 1995;114(7):1518–22.
281. Schlicker E, Betz R, Gothert M. Histamine H3 receptor-mediated inhibition of serotonin release in the rat brain cortex. Naunyn Schmiedebergs Arch Pharmacol. 1988;337(5):588–90.
282. Hill SJ, Ganellin CR, Timmerman H, et al. International Union of Pharmacology. XIII. Classification of histamine receptors. Pharmacol Rev. 1997;49(3):253–78.
283. Tokita S, Takahashi K, Kotani H. Recent advances in molecular pharmacology of the histamine systems: physiology and pharmacology of histamine H3 receptor: roles in feeding regulation and therapeutic potential for metabolic disorders. J Pharmacol Sci. 2006;101(1):12–8.
284. Wada H, Inagaki N, Itowi N, Yamatodani A. Histaminergic neuron system: morphological features and possible functions. Agents Actions Suppl. 1991;33:11–27.
285. Ito C. Histamine H3-receptor inverse agonists as novel antipsychotics. Cent Nerv Syst Agents Med Chem. 2009;9(2): 132–6.
286. Nakamura T, Itadani H, Hidaka Y, Ohta M, Tanaka K. Molecular cloning and characterization of a new human histamine receptor, HH4R. Biochem Biophys Res Commun. 2000;279(2): 615–20.
287. Coruzzi G, Pozzoli C, Adami M, et al. Strain-dependent effects of the histamine H(4) receptor antagonist JNJ7777120 in a murine model of acute skin inflammation. Exp Dermatol. 2012;21(1):32–7.
288. Hsieh GC, Chandran P, Salyers AK, et al. H4 receptor antagonism exhibits anti-nociceptive effects in inflammatory and neuropathic pain models in rats. Pharmacol Biochem Behav. 2010;95(1):41–50.
289. Flynn DD, Ferrari-DiLeo G, Mash DC, Levey AI. Differential regulation of molecular subtypes of muscarinic receptors in Alzheimer's disease. J Neurochem. 1995;64(4):1888–91.

290. Alcantara AA, Mrzljak L, Jakab RL, Levey AI, Hersch SM, Goldman-Rakic PS. Muscarinic m1 and m2 receptor proteins in local circuit and projection neurons of the primate striatum: anatomical evidence for cholinergic modulation of glutamatergic prefronto-striatal pathways. J Comp Neurol. 2001; 434(4):445–60.
291. Mrzljak L, Levey AI, Goldman-Rakic PS. Association of m1 and m2 muscarinic receptor proteins with asymmetric synapses in the primate cerebral cortex: morphological evidence for cholinergic modulation of excitatory neurotransmission. Proc Natl Acad Sci USA. 1993;90(11):5194–8.
292. Nathanson NM. Synthesis, trafficking, and localization of muscarinic acetylcholine receptors. Pharmacol Ther. 2008;119(1): 33–43.
293. Levey AI, Edmunds SM, Koliatsos V, Wiley RG, Heilman CJ. Expression of m1–m4 muscarinic acetylcholine receptor proteins in rat hippocampus and regulation by cholinergic innervation. J Neurosci. 1995;15(5 Pt 2):4077–92.
294. Rouse ST, Levey AI. Muscarinic acetylcholine receptor immunoreactivity after hippocampal commissural/associational pathway lesions: evidence for multiple presynaptic receptor subtypes. J Comp Neurol. 1997;380(3):382–94.
295. Volpicelli LA, Levey AI. Muscarinic acetylcholine receptor subtypes in cerebral cortex and hippocampus. Prog Brain Res. 2004;145:59–66.
296. Michal P, Lysikova M, El-Fakahany EE, Tucek S. Clozapine interaction with the M2 and M4 subtypes of muscarinic receptors. Eur J Pharmacol. 1999;376(1–2):119–25.
297. Olianas MC, Maullu C, Onali P. Mixed agonist-antagonist properties of clozapine at different human cloned muscarinic receptor subtypes expressed in Chinese hamster ovary cells. Neuropsychopharmacology. 1999;20(3):263–70.
298. Mrzljak L, Levey AI, Rakic P. Selective expression of m2 muscarinic receptor in the parvocellular channel of the primate visual cortex. Proc Natl Acad Sci USA. 1996;93(14):7337–40.
299. Mrzljak L, Levey AI, Belcher S, Goldman-Rakic PS. Localization of the m2 muscarinic acetylcholine receptor protein and mRNA in cortical neurons of the normal and cholinergically deafferented rhesus monkey. J Comp Neurol. 1998;390(1): 112–32.
300. Decossas M, Bloch B, Bernard V. Trafficking of the muscarinic m2 autoreceptor in cholinergic basalocortical neurons in vivo: differential regulation of plasma membrane receptor availability and intraneuronal localization in acetylcholinesterase-deficient and -inhibited mice. J Comp Neurol. 2003;462(3):302–14.
301. Bonsi P, Martella G, Cuomo D, et al. Loss of muscarinic autoreceptor function impairs long-term depression but not long-term potentiation in the striatum. J Neurosci. 2008;28(24): 6258–63.
302. Rouse ST, Edmunds SM, Yi H, Gilmor ML, Levey AI. Localization of M(2) muscarinic acetylcholine receptor protein in cholinergic and non-cholinergic terminals in rat hippocampus. Neurosci Lett. 2000;284(3):182–6.
303. Shen KZ, Johnson SW. Presynaptic dopamine D2 and muscarine M3 receptors inhibit excitatory and inhibitory transmission to rat subthalamic neurones in vitro. J Physiol. 2000;525(Pt 2): 331–41.
304. Vilaro MT, Palacios JM, Mengod G. Localization of m5 muscarinic receptor mRNA in rat brain examined by in situ hybridization histochemistry. Neurosci Lett. 1990;114(2):154–9.
305. Schambra UB, Mackensen GB, Stafford-Smith M, Haines DE, Schwinn DA. Neuron specific alpha-adrenergic receptor expression in human cerebellum: implications for emerging cerebellar roles in neurologic disease. Neuroscience. 2005;135(2):507–23.
306. Spreng M, Cotecchia S, Schenk F. A behavioral study of alpha-1b adrenergic receptor knockout mice: increased reaction to novelty and selectively reduced learning capacities. Neurobiol Learn Mem. 2001;75(2):214–29.
307. Watson M, McElligott JG. Cerebellar norepinephrine depletion and impaired acquisition of specific locomotor tasks in rats. Brain Res. 1984;296(1):129–38.
308. Arnsten AF. Adrenergic targets for the treatment of cognitive deficits in schizophrenia. Psychopharmacology (Berl). 2004;174(1):25–31.
309. van Kammen DP, Kelley M. Dopamine and norepinephrine activity in schizophrenia. An integrative perspective. Schizophr Res. 1991;4(2):173–91.
310. Baldessarini RJ, Huston-Lyons D, Campbell A, Marsh E, Cohen BM. Do central antiadrenergic actions contribute to the atypical properties of clozapine? Br J Psychiatry Suppl. 1992;17:12–6.
311. Woodward DJ, Moises HC, Waterhouse BD, Yeh HH, Cheun JE. The cerebellar norepinephrine system: inhibition, modulation, and gating. Prog Brain Res. 1991;88:331–41.
312. Birnbaum S, Gobeske KT, Auerbach J, Taylor JR, Arnsten AF. A role for norepinephrine in stress-induced cognitive deficits: alpha-1-adrenoceptor mediation in the prefrontal cortex. Biol Psychiatry. 1999;46(9):1266–74.
313. Arnsten AF, Mathew R, Ubriani R, Taylor JR, Li BM. Alpha-1 noradrenergic receptor stimulation impairs prefrontal cortical cognitive function. Biol Psychiatry. 1999;45(1):26–31.
314. Ferry B, Roozendaal B, McGaugh JL. Basolateral amygdala noradrenergic influences on memory storage are mediated by an interaction between beta- and alpha1-adrenoceptors. J Neurosci. 1999;19(12):5119–23.
315. Ferry B, Roozendaal B, McGaugh JL. Involvement of alpha1-adrenoceptors in the basolateral amygdala in modulation of memory storage. Eur J Pharmacol. 1999;372(1):9–16.
316. Ferry B, Roozendaal B, McGaugh JL. Role of norepinephrine in mediating stress hormone regulation of long-term memory storage: a critical involvement of the amygdala. Biol Psychiatry. 1999;46(9):1140–52.
317. Marshall I, Burt RP, Chapple CR. Noradrenaline contractions of human prostate mediated by alpha 1A-(alpha 1c-) adrenoceptor subtype. Br J Pharmacol. 1995;115(5):781–6.
318. Furukawa K, Rosario DJ, Smith DJ, Chapple CR, Uchiyama T, Chess-Williams R. Alpha 1A-adrenoceptor-mediated contractile responses of the human vas deferens. Br J Pharmacol. 1995;116(1):1605–10.
319. Moriyama N, Nasu K, Takeuchi T, et al. Quantification and distribution of alpha 1-adrenoceptor subtype mRNAs in human vas deferens: comparison with those of epididymal and pelvic portions. Br J Pharmacol. 1997;122(6):1009–14.
320. Docherty JR. Subtypes of functional alpha1- and alpha2-adrenoceptors. Eur J Pharmacol. 1998;361(1):1–15.
321. Devauges V, Sara SJ. Activation of the noradrenergic system facilitates an attentional shift in the rat. Behav Brain Res. 1990;39(1):19–28.
322. Arnsten AF, Goldman-Rakic PS. Alpha 2-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. Science. 1985;230(4731):1273–6.
323. Sara SJ, Dyon-Laurent C, Herve A. Novelty seeking behavior in the rat is dependent upon the integrity of the noradrenergic system. Brain Res Cogn Brain Res. 1995;2(3):181–7.
324. Lakhlani PP, MacMillan LB, Guo TZ, et al. Substitution of a mutant alpha2a-adrenergic receptor via "hit and run" gene targeting reveals the role of this subtype in sedative, analgesic, and anesthetic-sparing responses in vivo. Proc Natl Acad Sci USA. 1997;94(18):9950–5.
325. Yavich L, Lappalainen R, Sirvio J, Haapalinna A, MacDonald E. Alpha2-adrenergic control of dopamine overflow and metabolism in mouse striatum. Eur J Pharmacol. 1997;339(2–3):113–9.

326. Scheibner J, Trendelenburg AU, Hein L, Starke K. Alpha2-adrenoceptors modulating neuronal serotonin release: a study in alpha2-adrenoceptor subtype-deficient mice. Br J Pharmacol. 2001;132(4):925–33.
327. Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. Anesthesiology. 2000;93(5):1345–9.
328. Knaus AE, Muthig V, Schickinger S, et al. Alpha2-adrenoceptor subtypes–unexpected functions for receptors and ligands derived from gene-targeted mouse models. Neurochem Int. 2007; 51(5):277–81.
329. Franowicz JS, Arnsten AF. Actions of alpha-2 noradrenergic agonists on spatial working memory and blood pressure in rhesus monkeys appear to be mediated by the same receptor subtype. Psychopharmacology (Berl). 2002;162(3):304–12.
330. Franowicz JS, Arnsten AF. Treatment with the noradrenergic alpha-2 agonist clonidine, but not diazepam, improves spatial working memory in normal young rhesus monkeys. Neuropsychopharmacology. 1999;21(5):611–21.
331. Link RE, Desai K, Hein L, et al. Cardiovascular regulation in mice lacking alpha2-adrenergic receptor subtypes b and c. Science. 1996;273(5276):803–5.
332. Sallinen J, Haapalinna A, Viitamaa T, Kobilka BK, Scheinin M. Adrenergic alpha2C-receptors modulate the acoustic startle reflex, prepulse inhibition, and aggression in mice. J Neurosci. 1998;18(8):3035–42.
333. Imaki J, Mae Y, Shimizu S, Ohno Y. Therapeutic potential of alpha2 adrenoceptor antagonism for antipsychotic-induced extrapyramidal motor disorders. Neurosci Lett. 2009;454(2): 143–7.
334. Marcus MM, Wiker C, Franberg O, et al. Adjunctive alpha2-adrenoceptor blockade enhances the antipsychotic-like effect of risperidone and facilitates cortical dopaminergic and glutamatergic, NMDA receptor-mediated transmission. Int J Neuropsychopharmacol. 2010;13(7):891–903.
335. Kalkman HO, Loetscher E. alpha2C-Adrenoceptor blockade by clozapine and other antipsychotic drugs. Eur J Pharmacol. 2003;462(1–3):33–40.
336. Sallinen J, Link RE, Haapalinna A, et al. Genetic alteration of alpha 2C-adrenoceptor expression in mice: influence on locomotor, hypothermic, and neurochemical effects of dexmedetomidine, a subtype-nonselective alpha 2-adrenoceptor agonist. Mol Pharmacol. 1997;51(1):36–46.
337. Andrade R. Serotonergic regulation of neuronal excitability in the prefrontal cortex. Neuropharmacology. 2011;61(3):382–6.
338. Hagan RM, Kilpatrick GJ, Tyers MB. Interactions between 5-HT3 receptors and cerebral dopamine function: implications for the treatment of schizophrenia and psychoactive substance abuse. Psychopharmacology (Berl). 1993;112(1 Suppl):S68–75.