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Invited review

Antipsychotics: Mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology

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HIGHLIGHTS

- Striatal dopamine D2/3 receptor blockade is essential for clinical antipsychotic response but within a therapeutic window.
- Off target effects at serotonergic, histaminergic, cholinergic & adrenergic receptors are responsible for key side effects.
- Current drugs act downstream of the major dopamine abnormalities and may worsen cortical dopamine function.
- New approaches include targeting dopamine synthesis and capacity, autoreceptors, trace-amine receptors and other mechanisms.
- Non-dopmaminergic approaches such as those addressing inflammation may prove to be disease modifying.

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ABSTRACT

Antipsychotic drugs are central to the treatment of schizophrenia and other psychotic disorders but are ineffective for some patients and associated with side-effects and nonadherence in others. We review the in vitro, pre-clinical, clinical and molecular imaging evidence on the mode of action of antipsychotics and their side-effects. This identifies the key role of striatal dopamine D2 receptor blockade for clinical response, but also for endocrine and motor side-effects, indicating a therapeutic window for D2 blockade. We consider how partial D2/3 receptor agonists fit within this framework, and the role of off-target effects of antipsychotics, particularly at serotonergic, histaminergic, cholinergic, and adrenergic receptors for efficacy and side-effects such as weight gain, sedation and dysphoria. We review the neurobiology of schizophrenia relevant to the mode of action of antipsychotics, and for the identification of new treatment targets. This shows elevated striatal dopamine synthesis and release capacity in dorsal regions of the striatum underlies the positive symptoms of psychosis and suggests reduced dopamine release in cortical regions contributes to cognitive and negative symptoms. Current drugs act downstream of the major dopamine abnormalities in schizophrenia, and potentially worsen cortical dopamine function. We consider new approaches including targeting dopamine synthesis and storage, autoreceptors, and trace amine receptors, and the cannabinoid, muscarinic, GABAergic and glutamatergic regulation of dopamine neurons, as well as post-synaptic modulation through phosphodiesterase inhibitors. Finally, we consider treatments for cognitive and negative symptoms such dopamine agonists, nicotinic agents and AMPA modulators before discussing immunological approaches which may be disease modifying.

1. Introduction

Schizophrenia is a common mental disorder characterised by positive symptoms, such as delusions and hallucinations, negative symptoms such as avolition and social withdrawal, and cognitive impairments (Revier et al., 2015). It typically presents in late adolescence to early adulthood, starting with a prodromal phase of subtle changes in thinking and behaviour (Howes and Murray, 2014). Conservative estimates suggest that 21 million people are living with schizophrenia worldwide (Charlson et al., 2018) and that people with schizophrenia have a life expectancy around 15 years shorter than the general population (Hjorthoj et al., 2017). Antipsychotic drugs are effective in treating the acute manifestations of the illness and in reducing the risk of relapse (Leucht et al., 2017), yet side effects can be intolerable and lead to treatment discontinuation (Lieberman et al., 2005). Non-adherence rates are high amongst patients prescribed antipsychotics

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(Novick et al., 2010b) and this is a major risk factor for relapse and hospitalisation (Ascher-Svanum et al., 2006). For a significant proportion of patients their illness shows limited response to antipsychotics, which is termed treatment resistance (Howes et al., 2017). Treatment resistance is seen from illness onset in about 15% of patients, and in about one-third of patients overall (Lally et al., 2016). In this paper we first review the nature of the monoaminergic dysfunction in schizophrenia as this is core to understanding the mechanism of action of antipsychotic drugs. Then we consider receptor binding profiles of commonly used antipsychotic drugs, and discuss the mechanisms underlying their therapeutic action and side-effects. Finally, we consider the limitations of current antipsychotics and the implications for the development of future drug treatments for schizophrenia.

2. Monoamine systems and the pathophysiology of schizophrenia: in vivo neurotransmitter abnormalities

Schizophrenia is associated with many brain and other alterations, but here we focus on the main neurotransmitter systems relevant for understanding its treatment. Converging lines of evidence indicate that dopamine plays a key role in the pathophysiology of schizophrenia (Howes et al., 2015). Amphetamine causes dopamine release in healthy volunteers (Laruelle et al., 1995; Leyton et al., 2002) and induces schizophrenia-like psychotic symptoms (Connell, 1958; Griffith et al., 1972; Janowsky and Risch, 1979), which are attenuated by dopamine receptor blocking drugs (Curran et al., 2004). These psychotogenic effects of amphetamine are amplified in people with schizophrenia (Angrist et al., 1980; Lieberman et al., 1987) and molecular imaging techniques have shown that indexes of dopamine release in vivo, that is in healthy controls and patients, link dopamine release and the induction of psychotic symptoms by amphetamine (Howes et al., 2009a). Furthermore, people with schizophrenia have greater amphetamine or stress induced striatal dopamine release compared with healthy controls (Abi-Dargham et al., 1998; Breier et al., 1997; Mizrahi et al., 2012), and that greater striatal dopamine release is directly associated with greater induction of psychotic symptoms (Laruelle et al., 1999). Molecular imaging studies also find higher striatal dopamine synthesis and release capacity in patients with prodromal symptoms of psychosis (Howes et al., 2009c, 2011b; Mizrahi et al., 2012) and those with schizophrenia relative to matched controls (Hietala et al., 1995; Howes et al., 2013; Reith et al., 1994). Meta-analysis shows large effect size elevations in striatal dopamine synthesis and release capacity in schizophrenia (Howes et al., 2012). Moreover, higher striatal dopamine synthesis capacity in the prodrome to schizophrenia has been linked to the subsequent development of psychosis (Howes et al., 2011b), and found to increase during the progression to psychosis (Howes et al., 2011a). Synaptic dopamine levels have also been indexed in patients with schizophrenia using molecular imaging and a dopamine depletion paradigm, showing evidence for greater synaptic dopamine levels in the striata of patients with schizophrenia (Abi-Dargham et al., 2000; Howes et al., 2012; Slifstein et al., 2010). Moreover, striatal dopamine release and synaptic levels are directly related in schizophrenia (Abi-Dargham et al., 2009). Taken together, these findings indicate that the major striatal dopamine abnormalities found in psychosis are pre-synaptic and that excessive dopamine synthesis and release underlies positive symptoms (Howes and Kapur, 2009).

In contrast to findings in the striatum, molecular imaging evidence indicates blunted dopamine release in cortical regions in schizophrenia relative to controls (Rao et al., 2018; Slifstein et al., 2015). Moreover, blunted cortical dopamine release has been linked to poor performance on cognitive tasks in schizophrenia (Cassidy et al., 2016). Whilst cortical dopamine release warrants further testing in patients, these findings are consistent with long-standing hypotheses that cortical hypodopaminergia underlies cognitive symptoms and striatal hyperdopaminergia underlies psychosis in schizophrenia (Davis et al., 1991; Howes and Kapur, 2009).

Post-mortem studies in schizophrenia show increased dopamine receptor levels in subcortical and cortical brain regions in patients who largely received antipsychotic treatment over many years (Lee et al., 1978; Owen et al., 1978; Zakzanis and Hansen, 1998). Yet, molecular imaging studies show a different picture in vivo, with the possibility of an increase in striatal D2/3 receptors in some patients but no significant increase overall in antipsychotic naïve patients when the studies are meta-analysed (Howes et al., 2012) and no clear change in cortical dopamine D2/3 receptors either (Kambeitz et al., 2014). Importantly, there is also no in vivo evidence for altered dopamine D2/3 receptor internalisation following dopamine release in schizophrenia, indicating that this aspect of post-synaptic regulation of D2/3 receptors is not altered in the disorder (Weinstein et al., 2018). Taken together this suggests that the dopamine D2/3 receptor upregulation seen in post-mortem studies could be secondary to prior antipsychotic treatment or limited to a sub-group of patients (Howes et al., 2012; Mackay et al., 1980). Dopamine receptors also exist in high and low affinity states so people with schizophrenia may have an increase in the proportion of D2 receptors in the high affinity state (De Lean et al., 1982; Frankle et al., 2018; Sibley et al., 1982). This would mean that they are more sensitive to the effects of dopamine. However, the in vivo imaging evidence with a PET tracer that is selective for the high affinity form of the D2 receptor, has not supported this hypothesis to date (Graff-Guerrero et al., 2009).

After dopamine, the monoamine that has probably received the most investigation in schizophrenia is serotonin. The psychedelic effects of lysergic acid diethylamide (LSD), which binds to serotonin 2A receptors, coupled with post-mortem findings showing large alterations in brain levels of serotonin 2A and 1A receptors in schizophrenia, provide some support for a role of serotonin receptors in schizophrenia, although prior antipsychotic treatment may have confounded the post-mortem findings (Colpaert, 2003; Selvaraj et al., 2014; Shaw and Woolley, 1956). Moreover, studies of levels of serotonin and its metabolites in cerebrospinal fluid from patients are inconclusive (Abi-Dargham et al., 1997), and there is limited in vivo molecular imaging evidence to date (see review Selvaraj et al., 2014). Thus, overall, it is not clear if serotonergic alterations play a major role in the pathophysiology of schizophrenia, and further work is needed.

There is similarly limited evidence for a role of the adrenergic, cholinergic and histaminergic systems in the pathophysiology of schizophrenia. Post-mortem studies indicate that noradrenaline levels may be increased in patients relative to controls and elevated levels of noradrenaline in the cerebrospinal fluid (CSF) of patients has been associated with the positive symptoms of psychosis (Crow et al., 1979; Yamamoto and Hornykiewicz, 2004). Histamine 3 receptors, as measured by radioligand binding in post-mortem tissue, show evidence of up-regulation in the pre-frontal cortex, in patients compared with controls (Jin et al., 2009) and increased histamine metabolites in the CSF of patients with schizophrenia correlate with positive symptoms (Prell et al., 1995). One molecular neuroimaging study found lower levels of histamine 1 receptors in patients with schizophrenia compared with controls (Iwabuchi et al., 2005). Despite this limited evidence it is important to recognise the mixed aminergic actions of antipsychotics as discussed in the next section, in particular because they play an important role in side effect burden, but also because they may contribute to the therapeutic efficacy of antipsychotics by modulating dopamine activity, rather than by a direct action at these receptors (Bennett, 1998). We will discuss the role of the glutamate and GABA systems in schizophrenia in more detail below, in the section on novel treatments. First, we will explore the implications of the receptor affinities and occupancy levels of current antipsychotics for understanding their efficacy and side-effects.

3. Antipsychotics: main receptor binding profiles

The serendipitous discovery of chlorpromazine in the 1950s led to

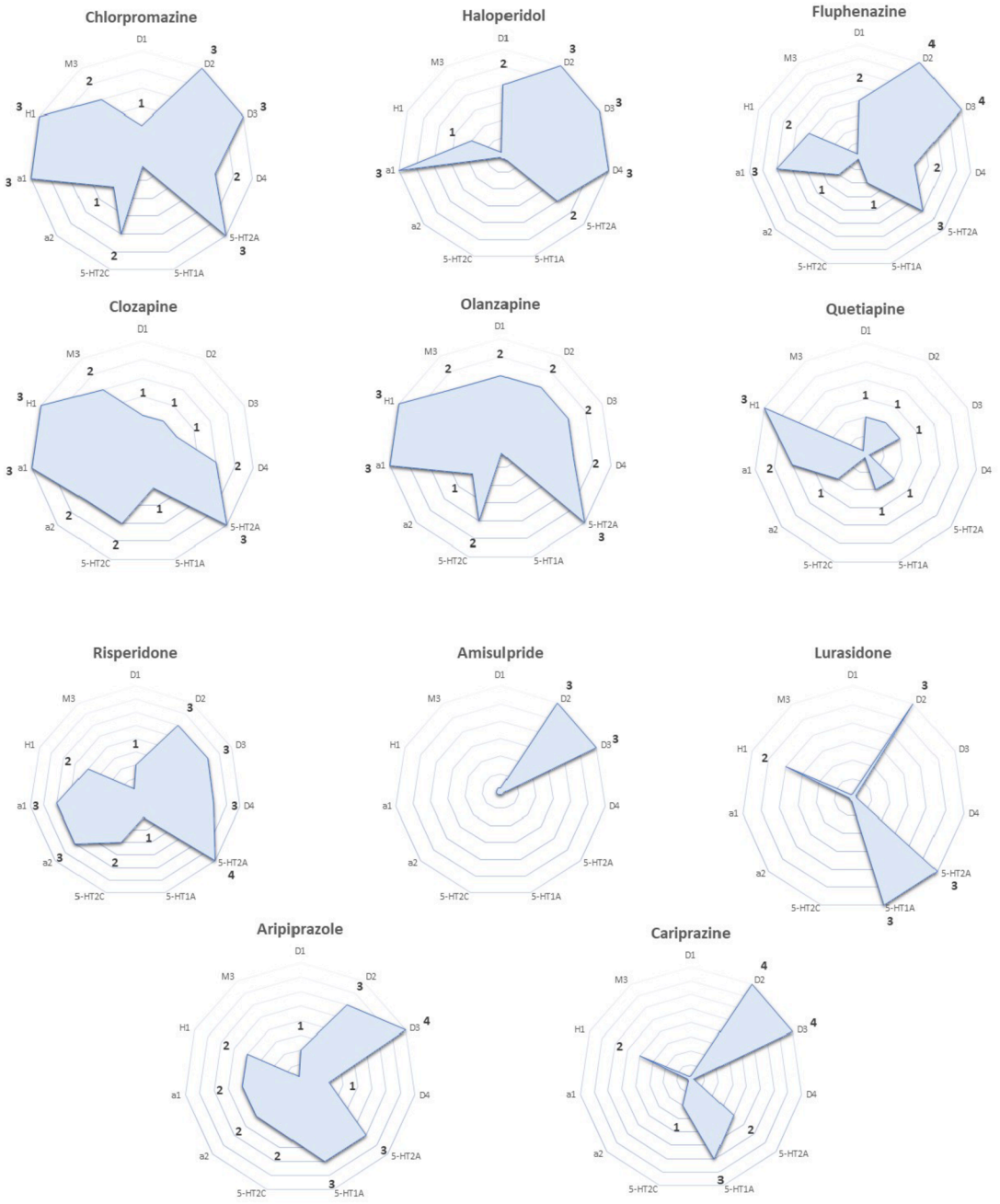

Fig. 1. The receptor affinities of commonly prescribed antipsychotics, showing that antipsychotic drugs vary markedly in their affinities for neuroreceptors. The numbers on the concentric lines represent the affinity (Ki) of a drug for that receptor where 4 = very high affinity (Ki < 1), 3 = high affinity (Ki 1–10), 2 = moderate affinity (Ki 10–100), 1 = low affinity (Ki 100–1000) and 0 = very low affinity (Ki > 1000). Data are the median Ki values from all human cloned Ki binding studies for each antipsychotic published on the National Institute of Mental Health's Psychoactive Drug Screening Program (PDSP) database https://pdsp.unc.edu/databases/kidb.php.

the design and development of the more than thirty different antipsychotic drugs now available in the clinic (Kapur et al., 2004). These drugs vary somewhat in the receptors they bind to (see Fig. 1), but all bind to dopamine D2/3 receptors to some degree (Howes et al., 2009a). Drug affinity for receptors can be considered in terms of the inhibition constant, Ki, which reflects the concentration of drug required to bind to 50% of the receptors in a competition binding assay. Thus, the inhibition constant Ki is an indicator of binding affinity: a lower value reflects a higher affinity of a drug for a given receptor (Yung-Chi and Prusoff, 1973). Table 1 shows the median Ki values calculated from the National Institute of Mental Health's Psychoactive Drug Screening Program (PDSP) database, and Fig. 1 shows this visually, for a number of representative antipsychotics. These data show that antipsychotics vary markedly in their affinities for neuroreceptors. However, all currently licensed antipsychotic drugs show appreciable binding to dopamine D2 receptors at therapeutic doses, and this action is core to their therapeutic action (Kapur et al., 2000; Nordstrom et al., 1993; Richtand et al., 2007; Seeman et al., 1976). In view of this, it is useful to consider their affinities at receptors relative to their affinity for D2 receptors. Fig. 2 shows the binding affinities in human cells lines (displayed as 1/Ki) of a range of representative antipsychotic drugs for the main neuroreceptors implicated in their therapeutic actions or common side-effects (using data from Table 1).

The discovery of haloperidol led to the development of several

Table 1
Median Ki values from all human cloned Ki binding studies for commonly prescribed antipsychotic drugs, using data published on the National Institute of Mental Health's Psychoactive Drug Screening Program (PDSP) database https://pdsp.unc.edu/databases/kidb.php.

	D1	D2	D3	D4	5-HT2A	5-HT1A	5-HT2C	α2	α1	H1	M3
Chlorpromazine	112.0	2.3	2.4	15.7	2.8	3057.5	15.6	281.8	1.4	2.8	57.0
Haloperidol	83.0	1.4	2.9	3.0	84.7	1808.0	5000.0	1202.3	4.7	851.1	> 1000
Fluphenazine	21.0	0.5	0.3	43.0	4.8	145.7	982.5	489.8	9.5	20.9	1441.0
Clozapine	192.5	119.0	242.0	29.5	6.5	140.0	15.2	33.1	4.0	1.8	25.0
Olanzapine	52.5	20.4	43.8	28.3	3.2	2063.0	12.1	173.8	55.0	2.4	78.0
Quetiapine	741.3	212.5	340.0	2100.0	200.0	320.0	1406.3	> 1000	15.0	8.7	1631.5
Risperidone	267.0	2.2	6.0	7.8	0.4	420.0	23.5	5.1	1.4	18.8	> 10000
Amisulpride	10001.0	2.2	2.4	2369.0	8304.0	> 10000	> 10000	1600.0	7100.0	> 10000	> 10000
Lurasidone	No data	1.7	No data	No data	2.0	6.8	No data	47.9	No data	> 1000	No data
Aripiprazole	387.0	1.4	1.0	216.5	8.7	5.6	18.7	72.4	27.6	29.0	4677.0
Cariprazine	No data	0.6	0.1	No data	19.0	3.0	134.0	No data	No data	23.0	No data

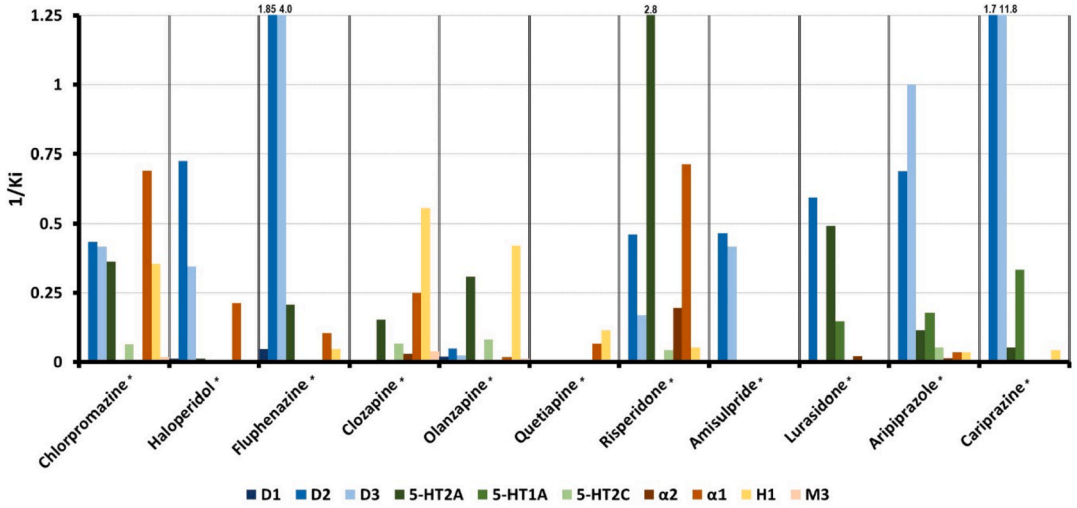

Fig. 2. Median Ki values of common antipsychotics displayed as 1/Ki on *y* axis (i.e.: higher values indicate a higher affinity). Data are the median Ki values from binding studies using human cell lines for each antipsychotic published on the National Institute of Mental Health's Psychoactive Drug Screening Program (PDSP) database (https://pdsp.unc.edu/databases/kidb.php). Data were not available on the PDSP database for cariprazine or lurasidone so values are taken from (Citrome, 2013a) and (Ishibashi et al., 2010) respectively. *indicates that other receptor affinities are reported but that the Ki value is > 10000 i.e. very weak affinity.

antipsychotics with a high affinity to the dopamine D2/3 receptor (e.g. fluphenazine highlighted in this review), many of which remain in clinical use today. Subsequently, the discovery that clozapine had greater efficacy, particularly for treatment resistance, and lower rates of motor side-effects, led to the development of the second generation of antipsychotics (e.g. risperidone, olanzapine, quetiapine, etc.) which attempted to reproduce its pharmacology (Seeman and Tallerico, 1998). Antipsychotics which act via partial agonism at the dopamine D2/3 receptors, such as aripiprazole, brexiprazole and cariprazine, represent the third generation of antipsychotics, and have a distinct mode of action that is discussed in the next section (Citrome, 2013b; Maeda et al., 2014; Natesan et al., 2011). Several agents show high serotonin 5-HT2A receptor affinity relative to dopamine D2/3 receptor blockade, for example risperidone, which has a particularly high affinity for 5-HT2A receptors. The following sections consider the role of antipsychotic actions at these receptors and others for their mode of action and side-effects.

4. Receptor occupancy and clinical response

4.1. Dopamine D2/3 receptor occupancy and clinical response

As discussed above, binding assays have established that all current antipsychotics bind to dopamine receptors. Moreover, in vitro antipsychotic dopamine D2 receptor affinity inversely correlates with the clinically effective dose (Creese et al., 1976; Seeman and Lee, 1975; Seeman et al., 1976). These studies provide a link between dopamine receptor occupancy and the clinical action of antipsychotic drugs. However, in-vivo studies were needed to test the link between dopamine receptor occupancy and clinical response. Molecular imaging studies are able to do this and show that striatal dopamine D2 receptor blockade is seen in vivo at clinically effective doses of all antipsychotic drugs including first and second-generation agents and dopamine partial agonists (Farde et al., 1988, 1992; Kapur et al., 1997, 1999; Nordstrom et al., 1993; Pilowsky et al., 1993; Stone et al., 2009). One implication of this finding is that if an antipsychotic drug shows a similar affinity for another receptor as its affinity for D2 receptors, then it is likely to show appreciable blockade of that receptor at clinical doses as well. Thus, it is useful to consider the affinities of antipsychotic drugs for receptors relative to their affinity for D2 receptors for understanding the potential mode of action and side-effect profiles of different drugs. Fig. 3 shows antipsychotic binding affinities for representative drugs relative to their dopamine D2 receptor affinity (1/(median Ki for the receptor/median Ki D2)). Clearly, when compared to the other antipsychotics, clozapine, olanzapine, quetiapine and risperidone have much higher affinities for other receptors relative to their dopamine D2 receptor affinities. Such antipsychotics with high affinities for receptors other than dopamine D2 will block a significant number of those receptors at clinically effective doses. For example, clozapine has higher affinities for histamine H1 receptors and alpha-1 adrenoceptors than D2 receptors. Consequently, at clinically effective doses, when it typically blocks > 40% of D2 receptors (Kapur et al., 1999; Nordstrom et al.,

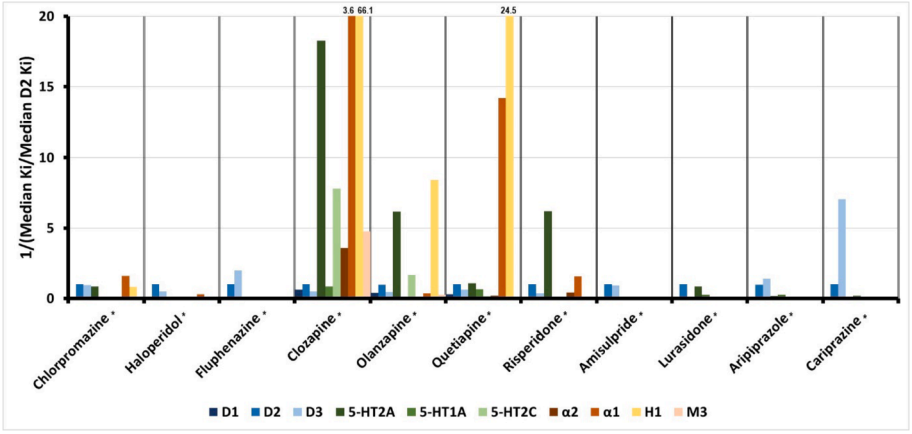

Fig. 3. Median Ki values relative to D2 affinity of common antipsychotics displayed as 1/(median Ki receptor/median Ki D2). Therefore, on *y* axis a higher value indicates a higher receptor affinity relative to its D2 affinity. Data are the median Ki values from all human cloned Ki binding studies for each antipsychotic published on the National Institute of Mental Health's Psychoactive Drug Screening Program (PDSP) database https://pdsp.unc.edu/databases/kidb.php. Data were not available on the PDSP database for cariprazine or lurasidone so values are taken from (Citrome, 2013a) and (Ishibashi et al., 2010) respectively. Note that not all receptor affinities are shown. For example, clozapine has high dopamine D4 receptor affinity (Van Tol et al., 1991) and amisulpride and lurasidone both have high affinities for serotonin 5HT7 receptors (Abbas et al., 2009; Ishibashi et al., 2010). *indicates that other receptor affinities are present but that the Ki value is > 10000 i.e. very weak affinity.

1995), there will be substantial occupancy of these other receptors as well, meaning that it is hard to avoid side-effects mediated by adrenoceptor blockade (Peacock et al., 1996) or histaminergic antagonism (see below for further discussion of side-effects).

In general, molecular imaging studies have shown that dopamine D2 receptor blockade above 50% occupancy is required for a high likelihood of clinical response whilst occupancy above about 85% increases the risk of extra-pyramidal side-effects (see section on side-effects and Howes et al. (2009b) (Kapur et al., 2000; Nyberg et al., 1995; Uchida et al., 2011). These findings indicate that there is a therapeutic window of between 60 and 80% D2 receptor occupancy that achieves a balance between a high likelihood of response with a low risk of motor side-effects, see Fig. 4. So far, only clozapine and dopamine partial agonists, such as aripiprazole, are exceptions to this rule. At clinically effective doses clozapine results in lower striatal dopamine D2 receptor occupancy of around 40% (Farde et al., 1992; Kapur et al., 1999; Nordström et al., 1993; Nordstrom et al., 1995), which has implications for its mode of action and side-effect profile (see below). In contrast, aripiprazole and cariprazine occupy a high proportion, 80% or more, of D2 receptors at therapeutic doses (Girgis et al., 2016a; Gründer et al., 2008; Mamo et al., 2007; Yokoi et al., 2002). It therefore seems that a higher D2 occupancy level is required for partial agonist antipsychotics than dopamine antagonists for a clinical effect, which may reflect the fact that unlike antagonists they have intrinsic activity at D2 receptors but this intrinsic activity is lower than that of dopamine, so results in net functional antagonism, similar to that seen with antagonists at clinically relevant doses (Girgis et al., 2016a; Gründer et al., 2008).

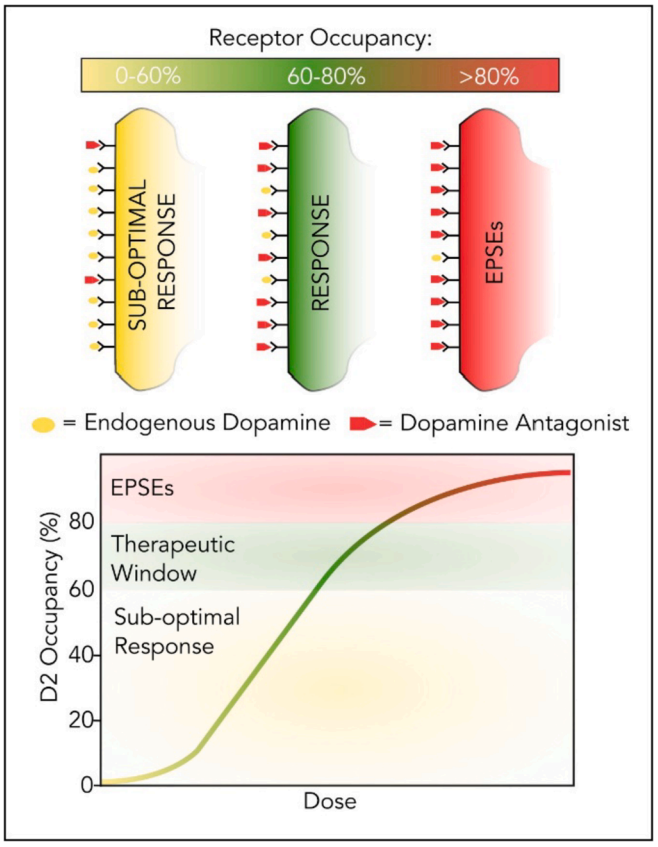

Fig. 4. The therapeutic window of dopamine D2 receptor occupancy for D2 antagonist antipsychotic drugs in schizophrenia, illustrating that antipsychotic dopamine D2 receptor occupancy of between 60 and 80% achieves a balance of a high likelihood of response with a low likelihood of motor side-effects, except in the case of dopamine D2 partial agonists which require higher occupancy levels.

4.2. Occupancy of other dopamine receptors and clinical response

Although dopamine D2/3 receptors are often considered together, there is evidence to support a role of D3 receptor binding in antipsychotic efficacy (Girgis et al., 2016a; Griffon et al., 1995). D3 receptors have a higher density in the ventral striatum and mesolimbic regions compared with dopamine D2 receptors (Gurevich and Joyce, 1999; Murray et al., 1994) and have an inhibitory effect on motor activity, the opposite of dopamine D2 receptors (Svensson et al., 1994). However, selective dopamine D3 antagonists do not appear to exert an antipsychotic effect (Redden et al., 2011), so it has been suggested that a balance between dopamine D2 and dopamine D3 blockade may offer optimum efficacy (Girgis et al., 2016a).

At clinically effective doses dopamine D1 receptor occupancy varies widely between antipsychotics, with occupancy levels of 0% seen with haloperidol, ~25% with risperidone and up to ~60% with clozapine (Farde et al., 1992; Nordstrom et al., 1995; Tauscher et al., 2004). Dopamine D1 receptors are thought to play a role in attention, working memory and executive function (Goldman-Rakic et al., 2004) and molecular imaging studies suggest abnormalities in dopamine D1 receptors in the pre-frontal cortex in untreated patients with schizophrenia correlate with impaired working-memory task performance (Abi-Dargham et al., 2002; Okubo et al., 1997). However, a subsequent study found evidence of dopamine D1 receptors upregulation in the cortex of drug-naïve patients with schizophrenia but not drug-free patients, yet this wasn't found to correlate with working memory performance, as measured by the *n*-back test (Abi-Dargham et al., 2012;

Cohen et al., 1994), and a recent larger study in drug naïve first episode psychosis patients found a higher density of dopamine D1 receptors in the pre-frontal cortex in patients (Stenkrona et al., 2018). Therefore, whether dopamine D1 receptors in the pre-frontal cortex are up or downregulated in the illness remains unclear (Howes et al., 2012; Kambeitz et al., 2014). Instead pre-synaptic hypodopaminergia in cortical regions in people with schizophrenia may account for the working memory deficits that are commonly found in the disorder (Aleman et al., 1999; Howes et al., 2009a; Slifstein et al., 2015). Furthermore, pure D1 receptor antagonists have not proved to be efficacious as antipsychotics and appear poorly tolerated in patients with schizophrenia (Karlsson et al., 1995). Similarly, pure dopamine D1 agonists, although better tolerated than D1 antagonists, have so far also demonstrated limited clinical efficacy (George et al., 2007; Girgis et al., 2016b; Rosell et al., 2015).

D4 receptors are found in similar brain regions to D2 receptors but probably at lower concentrations (Van Tol et al., 1991). Clozapine is unique in that it has a high affinity for D4 receptors relative to its dopamine D2 affinity (Van Tol et al., 1991) and so should occupy a higher proportion of dopamine D4 receptors at clinically effective doses than other antipsychotics. However, selective D4 receptor antagonists have not proved to be effective as antipsychotics to date (Bristow et al., 1997).

4.3. Occupancy at non-dopaminergic receptors and clinical response

The role of the serotonin 2A (5-HT2A) receptor in antipsychotic efficacy has been the focus of interest since the 1980s, when it was suggested that 5HT2A antagonism might contribute to clozapine's therapeutic effects (Meltzer, 1989). However, the contribution of serotonergic antagonism to antipsychotic efficacy remains controversial (Seeman, 2014). Molecular imaging has demonstrated that olanzapine has near 100% 5-HT2A occupancy at sub-therapeutic doses (Kapur et al., 1998), suggesting 5-HT2A occupancy is not related to its antipsychotic effect. Risperidone also shows high levels of 5-HT2A occupancy at low doses (Kapur et al., 1999; Nyberg et al., 1993), whereas aripiprazole exhibits lower 5-HT2A occupancy of around 50% at clinical doses and so is, similar to first-generation dopamine antagonists such as haloperidol (Mamo et al., 2007; Natesan et al., 2006). On the other hand, amisulpride shows negligible 5-HT2A binding but is ranked amongst the most effective antipsychotic drugs (Leucht et al., 2013). Moreover, pure 5-HT2A antagonists have proved ineffective in treating schizophrenia (de Paulis, 2001), notwithstanding some promising early findings (Meltzer et al., 2004). Thus, taken together, the evidence indicates 5HT2A antagonism is neither necessary nor a major contributor to antipsychotic action. However, post-mortem studies show large reductions in cortical 5HT2A receptor levels in schizophrenia (Selvaraj et al., 2014), and there is promising new evidence in support of the potential utility of 5-HT2A agents from studies of pimavanserin, which acts as an inverse agonist at 5-HT2A receptors (Meltzer et al., 2012). Pimavanserin has recently been licenced in the treatment of psychosis associated with Parkinson's disease (Schneider, 2018), and is currently being tested for schizophrenia. 5-HT1A agonism has been hypothesised to be important for the clinical efficacy of some antipsychotics (Meltzer and Huang, 2008), and moderate-large increases in 5HT1A levels are reported in frontal cortex in schizophrenia (Selvaraj et al., 2014). Adding 5HT1A partial agonists to antipsychotics has been associated with therapeutic benefits, suggesting 5HT1A agonism may play a role in clinical response, but studies to date have been small and findings inconsistent (Zheng et al., 2018). Two antipsychotics with high affinities for 5-HT1A receptors have been approved in the last three years: brexpiprazole, a D2 partial agonist, that acts as a partial agonist at 5-HT1A (Maeda et al., 2014) and cariprazine, a potent D3/2 receptor partial agonist and 5-HT1A receptor partial agonist (Marder et al., 2018). However, the contribution of 5HT1A agonism to their therapeutic actions in patients remains to be determined.

As can be seen from Fig. 3 clozapine, olanzapine and quetiapine have high affinities for histamine H1 receptors relative to their dopamine D2 receptor binding. Such affinity levels are thought to be responsible for side effects such as sedation, which has been linked to higher levels of histamine H1 occupancy in antihistamines (Tagawa et al., 2001; Yanai and Tashiro, 2007), and is discussed further in the next section, but whether such binding improves their antipsychotic efficacy is less understood. Sedation can be beneficial in the treatment of acute episodes of psychosis and some medications with high levels of antihistaminergic activity including olanzapine and promethazine are efficacious in reducing acute agitation in psychosis (Patel et al., 2018; Raveendran et al., 2007). Clozapine is a very potent partial histamine H1 receptor agonist, a weak, full inverse agonist at histamine H2 receptors, a moderate H3 agonist and a moderate partial H4 agonist (Humbert-Claude et al., 2012) and is uniquely efficacious (Kane et al., 1988; Tiihonen et al., 2019). Interestingly, a single randomised control trial of the histamine H2 agonist famotidine showed improvements in positive symptoms and general functioning in patients with schizophrenia (Meskanen et al., 2013), though a subsequent meta-analysis of histamine H2 receptor agonist trials in schizophrenia did not find any improvement in overall symptoms (Kishi and Iwata, 2015). Histamine H3 receptor antagonists have been explored in the treatment of the cognitive symptoms of schizophrenia, which are discussed in more detail below, but have been unsuccessful thus far (Jarskog et al., 2015).

5. Receptor binding and side effects

5.1. Extrapyramidal side-effects

Extra-pyramidal side-effects (EPSE) of antipsychotics such as akathisia, acute dystonias, parkinsonianism and tardive dyskinesia are common, affecting 10%–35% of patients (Novick et al., 2010a). Dopamine D2 receptor blockade appears to be required for the development of EPSE as demonstrated by the absence of haloperidol-induced catalepsy in dopamine D2 receptor knock out mice (Boulay et al., 2000). Moreover, in vivo PET occupancy studies show that the risk of EPSE increases significantly when dopamine D2 receptor occupancy is over 80% (Farde et al., 1992; Kapur et al., 2000; Nordstrom et al., 1993). The risk of EPSE can therefore be minimised by choosing a dose that avoids high dopamine D2 receptor occupancy whilst achieving sufficient D2/3 receptor blockade, for a high likelihood of clinical response (see section on clinical response). The licensed dose ranges of second generation antipsychotics typically do this (de Haan et al., 2003; Kapur et al., 2000), with the exception of partial agonists such as aripiprazole, which generally results in occupancy > 80% at clinically effective doses (Kegeles et al., 2008; Mamo et al., 2007). Despite such high dopamine D2 occupancy, aripiprazole does appear to have a lower propensity to cause EPSE than dopamine antagonists such as haloperidol (Kane et al., 2002), and preclinical models show it does not appear to induce catalepsy, unlike dopamine antagonists (Natesan et al., 2006). This could be due to its intrinsic activity at dopamine receptors, estimated at about 20% that of dopamine (Burris et al., 2002; Natesan et al., 2006). This is thought to ensure enough dopamine transmission to avoid catalepsy and reduce the risk of EPSE. This should also be the case for other partial agonists, such as caripiprizine and brexiprazole, although the degree of partial agonism varies from drug to drug. Clozapine has the lowest risk of EPSE amongst first and second generation agents (Leucht et al., 2013), which is thought to be due to its low dopamine D2 occupancy at clinically effective doses (Kapur et al., 1999) and its fast dissociation from the dopamine D2 receptor (Kapur and Seeman, 2000).

Serotonin 2A receptor blockade was thought to be protective against EPSE in the past. However, risperidone has a high affinity for serotonin 5-HT2A receptors and has a similar extrapyramidal side effect (EPSE) risk to amisulpride (Rummel-Kluge et al., 2012), which is relatively selective for dopamine D2/3 receptors (see Figs. 1 and 2), suggesting

that 5HT2A antagonism makes little difference, at least in the case of risperidone.

5-HT1A receptor stimulation reduces dopamine D2 antagonist-induced catalepsy in preclinical models (Invernizzi et al., 1988; Wadenberg et al., 1994), which suggests that 5-HT1A agonism could be important in reducing EPSE. Clozapine has a moderate affinity for 5-HT1a receptors (Newman-Tancredi et al., 1996) and a low propensity for EPSE (Leucht et al., 2013). However, at clinical doses clozapine does not significantly occupy 5-HT1A receptors in patients (Bantick et al., 2004), and a human study failed to demonstrate that 5-HT1A agonism increased striatal dopamine release, which was thought to be the mechanism by which such agonism reduced EPSE (Bantick et al., 2005).

Tardive dyskinesia is hypothesised to be secondary to dopamine receptor changes induced by long term dopamine blockade during antipsychotic treatment (Casey, 2004; Teo et al., 2012). Supporting this, long-term treatment with antipsychotics has been associated with higher dopamine D2/3 receptor availability in patients with tardive dyskinesia (Silvestri et al., 2000), although it should be recognised that this study has yet to be replicated and the sample also included treatment resistant patients. Nevertheless, this is consistent with preclinical models (Burt et al., 1977), which also indicate that chronic antipsychotic treatment increases dopamine D2/3 receptor levels (Calabresi et al., 1992). Furthermore, antipsychotic treatment may increase the proportion of dopamine D2 receptors in a high affinity state for dopamine (Samaha et al., 2007). Therefore, in some patients, chronic antipsychotic treatment may induce a relative striatal dopamine receptor hypersensitivity through increases in receptor levels and/or shifts in affinity states that leads to tardive dyskinesia. Interestingly vesicular monoamine transporter 2 (VMAT-2) inhibitors, discussed further below, improve the symptoms of tardive dyskinesia (Solmi et al., 2018b). VMAT-2 uptake of cytoplasmic dopamine into pre-synaptic vesicles is a key pathway in the storage of dopamine ready for release, and it is thought that VMAT-2 inhibition thus reduces dopamine release to reduce dyskinetic movements (Erickson et al., 1996; Liu and Edwards, 1997).

5.2. Endocrine side-effects

Prolactin is a polypeptide hormone secreted by the anterior pituitary gland under the control of dopamine neurons in the tuber-infundibular pathway (Bole-Feysot et al., 1998). Dopamine acting via dopamine D2 receptors has a direct inhibitory effect on lactotroph cells by supressing prolactin gene expression and prolactin exocytosis (Caron et al., 1978; Enjalbert and Bockaert, 1983). Dopamine D2 receptor antagonism, therefore, can lead to increased plasma prolactin levels due to blocking this feedback mechanism (Donoso et al., 1971; Rubin and Hays, 1980). Hyperprolactinemia occurs in approximately 20–40% of patients treated with antipsychotic medication, with higher rates in women than men (Howes et al., 2006; Johnsen et al., 2008; Lally et al., 2017). In vivo imaging studies demonstrate that raised prolactin in patients treated with D2/3 antagonist antipsychotics drugs correlates strongly with dopamine D2 receptor blockade, with > 75% receptor occupancy associated with a high likelihood of hyperprolactinemia (Kapur et al., 2000; Nordstrom and Farde, 1998; Shitij Kapur et al., 2001). This is not the case with partial agonists such as aripiprazole, where the partial agonism at D2/3 receptors inhibits prolactin secretion (Aihara et al., 2004). When aripiprazole is added to a dopamine antagonist, this is often sufficient to reduce hyperprolactinaemia (Kotorki et al., 2010; Shim et al., 2007). This has been attributed to high affinity of aripiprazole to dopamine D2/3 receptors compared to dopamine antagonists along with its D2/3 receptor partial agonism, which means it provides some stimulation of D2 receptors in the pituitary lactotrophs to inhibit prolactin release (Aihara et al., 2004). Clozapine has a lower risk of hyperprolactinaemia than other dopamine antagonists, which again is most likely because of its lower dopamine D2 occupancy (Kapur et al., 1999) and fast dissociation from the receptor (Kapur and Seeman, 2000). Antipsychotics with relatively poor blood brain penetrance, such as amisulpride, paliperidone and risperidone, require relatively higher doses to reach the necessary brain dopamine D2 receptor occupancy for a clinical effect than drugs with high brain penetrance, and so have high levels of D2 occupancy in the pituitary gland (Kapur et al., 2002), which lies outside the blood brain barrier. This goes some way to explain their greater propensity to cause hyperprolactinemia than other drugs.

5.3. Secondary negative symptoms

Antipsychotic drugs have the potential to cause secondary negative symptoms such as dysphoria and other subjective effects that are associated with a poor clinical outcome (Voruganti and Awad, 2004). Lower subjective well-being, a concept that includes mental functioning, self-control, emotional regulation, physical functioning, and social integration, as measured by the 'subjective well-being under neuroleptics' scale (SWN) (Naber et al., 2001), has been associated with higher levels of dopamine receptor occupancy in striatal, temporal and insular regions (Mizrahi et al., 2007). In particular, striatal occupancy levels above 70% correlate with lower self-report scores on the SWN (de Haan et al., 2003). In addition, akinesia or bradykinesia (Rifkin et al., 1975) secondary to antipsychotic medication, which can manifest as secondary negative symptoms such as diminished expression (Kirschner et al., 2017), is more likely to occur with D2 receptor occupancies over 60–80% (Farde et al., 1992; Knable et al., 1997). This suggests that in some cases a dose reduction may improve secondary negative symptoms and subjective well-being. It is important to recognise that some studies report a worsening of negative symptoms associated with antipsychotic withdrawal, which may reflect the multiple aetiologies underlying these symptoms (Miller et al., 1994; Naber et al., 1985). Sedation, through the mechanisms described below, may also be a secondary cause of amotivation associated with antipsychotic medication (Kirschner et al., 2017).

5.4. Weight gain and metabolic side effects

Trial data shows that patients with schizophrenia can gain between < 1 kg and > 4 kg over 10 weeks of treatment with an antipsychotic medication, depending on the drug (Allison et al., 1999). Olanzapine and clozapine carry the greatest risk, though other second-generation medications such as risperidone, paliperidone and to a lesser extent amisulpride and aripiprazole are also associated with weight gain (Leucht et al., 2013). Several actions of antipsychotic drugs, both dopaminergic and others, could contribute to weight gain. Preclinical models indicate that dopamine D2/3 receptor blockade can potentially disrupt both reward signalling associated with food consumption and satiation signalling (Parada et al., 1988). Clinical evidence for this comes from a study of amisulpride, which is a relatively selective dopamine D/3 receptor antagonist, showing that weight gain on amisulpride correlates with change in brain activity in the right-sided putamen to rewarding stimuli in patients with schizophrenia (Nielsen et al., 2016). This study supports the idea that dopamine-based reward anticipation may underlie antipsychotic induced weight gain rather than antipsychotic action at other receptors (Grimm et al., 2017). Olanzapine also alters striatal reward activation in response to food stimuli which appears to correlate with food consumption and eating disinhibition (Mathews et al., 2012). In contrast, brain responses to food stimuli are unaltered in antipsychotic free patients with schizophrenia relative to controls (Borgan et al., 2019), suggesting that alterations are antipsychotic related. Together these data suggest that dopamine related reward pathways are disrupted in people treated with antipsychotic drugs and that the disruption may lead to changes in food consumption and weight gain, though the magnitude of the effect of dopamine on weight gain compared to other neurotransmitter pathways is not yet known.

Dopamine D2/3 receptor blockade is not the only mechanism implicated in antipsychotic induced weight gain. As shown in Fig. 1, a number of antipsychotics have high affinities for histamine H1 receptors. H1 affinity significantly correlates with short-term weight gain during antipsychotic treatment (Kroeze et al., 2003), in particular with olanzapine and clozapine. Preclinical models support histamine H1 receptor blockade as being a key mechanism responsible for weight gain with olanzapine and clozapine (Kim et al., 2007), likely through activation of hypothalamic AMP-kinase, resulting in increased food intake (Masaki and Yoshimatsu, 2006; Minokoshi et al., 2004). Serotonin 5-HT2 receptor blockade is also linked to weight gain (Parsons et al., 2009). As can be seen in Fig. 2, both olanzapine and clozapine have high relative affinities for both serotonin 5-HT2A and 2C receptors. Clozapine is also associated with altered glucose homeostasis and hyperglycemia (Howes et al., 2004). Serotonin 5-HT2A knockout mice do not develop hyperglycaemia on clozapine, which suggests blockade of 5-HT2A receptors by clozapine may mediate its glucose dysregulatory effects (Joshi et al., 2018). The role of 5-HT2C receptor in feeding behaviour is well established (Bonhaus et al., 1997; Tecott et al., 1995; Vickers et al., 2001). Serotonin 5-HT2C knockout mice become obese due to abnormal control of feeding behaviour (Tecott et al., 1995) and recently 5-HT2C antagonism was shown to explain some of the weight gain associated with olanzapine (Lord et al., 2017). Furthermore, genetic polymorphisms in the serotonin 5-HT2C receptor appear to be associated with an increase in antipsychotic induced weight gain (Reynolds et al., 2002). Variations in the 5-HT2C gene, especially the −759C/T polymorphism, have emerged as promising candidates for prediction of antipsychotic-induced weight gain (Reynolds et al., 2002; Wallace et al., 2011). However, asenapine, an antipsychotic licenced for the treatment of schizophrenia in the US but not in Europe, has a very high 5-HT2C affinity and is associated with less weight gain than olanzapine, highlighting that the 5-HT2C actions of olanzapine are unlikely to explain all the weight gain seen with the drug (Kemp et al., 2014). Overall, given that olanzapine and clozapine block histamine H1, and serotonin 5-HT2A/C receptors as well as blocking dopamine D2/3 receptors, which are all mechanisms linked to weight gain, it is not surprising then that these drugs are associated with the greatest weight gain amongst antipsychotics (Leucht et al., 2013). In contrast, dopamine antagonists with little or no histaminergic or serotonergic activity, such as lurasidone, and dopamine partial agonists such as aripiprazole tend to have lower risks of weight gain and metabolic side effects (Rummel-Kluge et al., 2010).

5.5. Sedation

Sedation is a common complaint of patients taking antipsychotics (Arvanitis and Miller, 1997; Beasley et al., 1996; Kane et al., 1988; Marder and Meibach, 1994). Histamine H1 antagonism is a major contributor to sedation (Reiner and Kamondi, 1994). As shown in Fig. 2 clozapine, quetiapine, olanzapine and chlorpromazine, have the highest histamine H1 receptor affinity relative to their dopamine D2 receptor affinity, and these are the antipsychotics most associated with sedation, whereas drugs such as amisulpride, which have little affinity for H1 receptors (Fig. 1), are not associated with sedation (Leucht et al., 2013).

5.6. Dry eyes and mouth, visual and gastro-intestinal disturbance, and other anticholinergic effects

Fig. 1 shows that several antipsychotics have significant anticholinergic effects. Peripheral effects of cholinergic blockade include reduced salivation, bronchial secretions and sweating, increased pupil size and the inhibition of the accommodation reflex, tachycardia, urinary retention and constipation (Lieberman, 2004). Central effects of cholinergic blockade include impaired cognitive impairment and delirium (Minzenberg et al., 2004). Clozapine and olanzapine have high affinity for muscarinic receptors, specifically M1, and M3-5 receptors (Bolden et al., 1992; Bymaster et al., 1996). Clozapine may have partial agonist properties at some muscarinic receptors so can paradoxically induce sialorrhoea (Olianas et al., 1997; Zeng et al., 1997).

5.7. Other side-effects

Postural hypotension occurs in up to ~25% of patients treated with antipsychotic medication (Stroup et al., 2009) and is linked to the degree to which an antipsychotic drug antagonises α1-adrenoceptors (Haddad and Sharma, 2007). As can be seen in Fig. 2 clozapine and quetiapine have high affinity for alpha-1 adrenoceptors relative to their dopamine D2 receptor binding affinity, which explains why they carry the greatest risk of postural hypotension (McEvoy et al., 2006; Stroup et al., 2009). QTc prolongation is thought to be a marker of an increased risk of arrhythmias such as torsade de pointes and sudden cardiac death. Dopamine antagonists, and other drugs that can increase QTc, exert this effect in a dose related fashion by antagonism of potassium channels on cardiac myocytes leading to delayed repolarisation (Haddad and Anderson, 2002). Most antipsychotics can cause QTc prolongation but, amongst commonly used drugs, haloperidol, quetiapine and risperidone have a relatively high risk whereas aripiprazole and lurasidone have relatively low risks of affecting the QTc interval (Haddad and Anderson, 2002). Finally, there is evidence to suggest that long term antipsychotic treatment could lead to supersensitivity of the dopamine system, for example through the upregulation of dopamine receptors (Howes et al., 2012) and/or increases in the proportion of high affinity dopamine receptors (Seeman, 2013). This could mean that, over time, a stable dose of antipsychotic no longer provides sufficient dopamine blockade to counter the effects of hyperdopaminergia, resulting in break through symptoms and relapses despite treatment concordance (Chouinard and Chouinard, 2008; Samaha et al., 2007).

6. Implications for developing new drugs: *regulating dopamine function*

The evidence discussed above indicates that current antipsychotics primarily act by blocking dopamine receptors, which are largely downstream of the main dopamine abnormalities. Moreover, antipsychotics do not normalise the dopamine abnormalities (Jauhar et al., 2019). Dopamine blockade reduces aberrant dopamine signalling but also interferes with physiological signalling that is essential for adaptive learning, motivated behaviour, motor and other functions, leading to some of the side-effects discussed above and non-adherence. Thus, it would be preferable to target the dopamine abnormality itself to correct dysregulated striatal dopamine synthesis and release whilst permitting normal, physiological dopaminergic function in the striatum and cortex (see Fig. 5). There is proof of concept that this approach could be effective. Reserpine, an alkaloid extracted from the root of *Rauwolfia serpentina*, is an effective antipsychotic, and acts by inhibiting the uptake of dopamine by vesicular monoamine transporter 2 (VMAT2) into storage vesicles located in the presynaptic neuron to deplete dopamine stores (Braun, 1960; Yaffe et al., 2018). Similarly, alpha-methyl-p-tyrosine, an inhibitor of the rate-limiting enzyme in dopamine synthesis, reduces psychotic symptoms (Abi-Dargham et al., 2000). Abi-Dargham et al. (2000) showed this effect is linked to dopamine depletion. Unfortunately, these agents are poorly tolerated because they also block synthesis of other neurotransmitters, which has limited their use in clinical practice and highlights the need for selective agents.

Another strategy could be to target the regulation of dopamine system. Activation of dopamine D2 autoreceptors expressed on dopamine neurons (Fig. 5) reduces dopamine neuron firing and dopamine release (Mercuri et al., 1997; Suaud-Chagny et al., 1991). It is thought that apomorphine used at a low dose can be used to target dopamine autoreceptors whilst avoiding significant stimulation of post-synaptic D2 receptors (Meltzer, 1980). There is some evidence this is effective in treating schizophrenia (Tamminga et al., 1978; Zetterström and

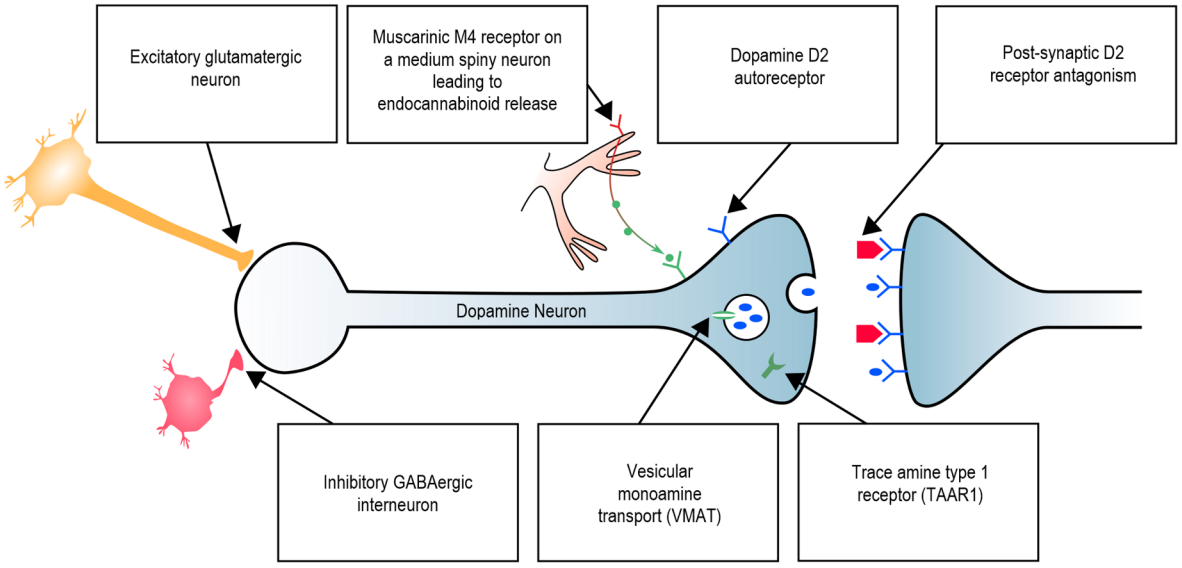

Fig. 5. Potential new treatment targets in schizophrenia. The figure shows current antipsychotics primarily act at D2 receptors downstream of the main dopamine abnormalities in schizophrenia and summarises alternative, potential mechanisms to regulate dopamine neuron function. Blocking the vesicular monoamine transporter, activating dopamine D2 autoreceptors or trace amine type 1 receptors, or modulating the retrograde activation of cannabinoid type 1 receptors by endocannabinoids are approaches that could directly target presynaptic dopamine dysregulation. Alternatively, targeting the upstream regulation of dopamine neuron activity via gamma aminobutyric (GABA)ergic or glutamatergic projections could be used to normalise dopamine neuron function.
Legend: = dopamine = dopamine D2 antagonist = dopamine receptor.

Ungerstedt, 1984), though subsequent studies were inconsistent, potentially because of post-synaptic effects at higher doses stimulating dopamine receptors to worsen psychosis in some patients (Levy et al., 1984). Jauhar et al. (2017b) used a lower dose than these clinical studies to show that apomorphine reduces striatal dopamine synthesis capacity in individuals with higher dopamine synthesis and increases it in people with lower dopamine synthesis. This suggests the autoreceptor approach could reduce striatal hyperdopaminergia to treat psychosis, whilst boosting dopamine function in regions with low dopamine function, potentially normalising cortical hypodopaminergia and treat cognitive symptoms. However, it remains to be determined if this approach will boost cortical dopamine levels.

D1 receptors, when activated, stimulate cyclic adenosine monophosphate (cAMP) while, in contrast, activation of dopamine D2 receptors inhibits cAMP production (Beaulieu et al., 2015). By reducing cAMP break down, phosphodiesterase (PDE) inhibitors may, thus, boost D1 signalling whilst inhibiting D2 signalling (Heckman et al., 2018). In this way, hypodopaminergia seen in cortical regions, where D1 receptors predominate, could be alleviated by increasing cAMP levels, whilst hyperdopaminergia seen in striatal regions, where dopamine D2 receptors predominate, could be addressed by also increasing cAMP levels to counter the effects of D2 stimulation (Menniti et al., 2006). There are 11 different PDE families, with each family typically having several different isoforms and splice variants (Francis et al., 2011). These unique PDEs differ in their properties, modes of regulation, intracellular localization, cellular expression, and inhibitor sensitivities (Bender and Beavo, 2006). The three main subtypes that are located in the coticostriatal and hippocampal circuits include PDE1B, PDE4 and PDE10A (Heckman et al., 2016). Rolipram was the prototype PDE4 inhibitor evaluated for psychiatric conditions, but its dose limiting side effects prevented further development (Kanes et al., 2007; Siuciak et al., 2007). However, isoform selective PDE4 inhibitors, that have less dose limiting side effects, such as roflumilast, are currently under development (Van Duinen et al., 2018). The PDE10A inhibitors were next to be evaluated for their efficacy in schizophrenia (Kehler and Nielsen, 2011). PDE10A is expressed in the striatum, hippocampus and in the cortex as well and inhibitors of this enzyme showed antipsychotic potential in preclinical studies (Coskran et al., 2006; Grauer et al., 2009). However, after the prototype PDE10A inhibitor, PF-02545920 developed by Pfizer, failed to show efficacy, development of this class of inhibitors has slowed down, but there are other promising PDE10A inhibitors that promise still in development (Macek et al., 2018). PDE1B is highly colocalized with D1 receptors in the brain and is particularly rich in the striatum, hippocampus, and prefrontal cortex (Lakics et al., 2010). Selective PDE1B modulators, including ITI-214 developed by Intra-Cellular Therapies, are currently undergoing evaluation for treating schizophrenia (ClinicalTrials.gov Identifier: NCT01900522) (Li et al., 2016).

Dopamine neurons are also under feedback control from trace amine type 1 receptors (TAAR1, see Fig. 5), which respond to endogenous amines such as tyramine and β-phenylethylamine (Lindemann et al., 2008). TAAR1 agonists reduce midbrain dopamine neuron activity (Revel et al., 2011a), reduce the hyperlocomotor response to stimulants (Revel et al., 2011b), and reduce evoked dopamine release (Leo et al., 2014; Revel et al., 2011b). These promising preclinical findings suggest that TAAR1 agonists may be able to target striatal hyperdopaminergia. Clinical trials using TAAR1 agonists are under way and should read out in the next few years.

6.1. Modulating dopamine via the glutamate and GABA systems

Another strategy might be to modulate the upstream glutamate and GABA systems that regulate dopamine neurons (Fig. 5). Ketamine induces psychotic symptoms similar to those seen in schizophrenia (Lahti et al., 1995), and this is thought to be due to its action as a non-competitive channel blocker of the *N*-methyl- D-aspartate (NMDA) glutamate receptor (Krystal et al., 1994). It is also associated with increases in amphetamine-induced striatal dopamine release, suggesting NMDA hypofunction could dysregulate dopamine release (Kegeles et al., 2000; Kokkinou et al., 2018). There is also some in vivo evidence of reduced NMDA receptor availability in schizophrenia (Pilowsky et al., 2006). These findings support the hypothesis that NMDA hypofunction is an upstream factor underlying dopamine dysfunction and psychosis (Howes et al., 2015; Javitt et al., 2012; Uno and Coyle, 2019). There is proof-of-concept that co-agonists at the NMDA receptor, such as serine and D-cycloserine, which promote channel opening to augment NMDA

receptor function, are effective in schizophrenia (Goff, 2015; Singh and Singh, 2011). However, the results of clinical trials have been inconsistent and it may be difficult to achieve high enough brain levels of these co-agonists to be effective (Goff, 2015). Glycine is an endogenous co-agonist at the NMDA receptor, and glycine transporter inhibitors have been developed as an alternative strategy to boost NMDA transmission (Goff, 2015). Unfortunately, the results of the clinical trials of glycine transporter inhibitors to date have been disappointing (Bugarski-Kirola et al., 2016). There is evidence for an inverted U-shaped dose response curve with glycine transporter inhibitors, which may have contributed to the disappointing results in trials to date, and studies are now evaluating the optimal brain occupancy of the glycine transporter for clinical benefit (D'Souza et al., 2018). Evenamide (NW-3509A), a potent anti-epileptic, is a selective inhibitor of voltage gated sodium channels and attenuates the stimulated release of glutamate downstream, as shown in in-vivo micro-dialysis (Anand et al., 2017). It has been shown to be effective in animal models of psychosis, mood disorders, aggression, negative symptoms, and cognitive dysfunction, both as monotherapy and as add-on treatment (Anand et al., 2017). Whilst, this strategy remains to be trialled in patients, sodium valproate, another sodium channel blocker, is commonly to augment antipsychotics in patients who have residual positive symptoms with some success (Wang et al., 2016), suggesting this approach may be effective.

In addition to glutamatergic dysfunction, GABAergic hypofunction is thought to play a role in the dopamine dysregulation found in schizophrenia (Lewis, 2000). Supporting this, post-mortem evidence shows lower levels of the GABA synthesising enzyme glutamate decarboxylase 67 (GAD67) (Curley et al., 2011; Guidotti et al., 2000; Hashimoto et al., 2008; Volk et al., 2000) and some studies show lower levels of parvalbumin containing GABAergic interneurons in schizophrenia, particularly in brain regions such as the pre-frontal cortex and the hippocampus though overall the post-mortem results on parvalbumin-containing neuronal loss are mixed (Beasley and Reynolds, 1997; Enwright et al., 2016; Hashimoto et al., 2003; Konradi et al., 2011; Tooney and Chahl, 2004; Woo et al., 1997). In addition parvalbumin containing GABAergic interneurons also exhibit reductions in parvalbumin protein and mRNA and other molecular abnormalities in people with schizophrenia (Chung et al., 2016; Fung et al., 2014; Glausier et al., 2014; Mellios et al., 2009; Volk et al., 2016a, 2016b). As off target effects are dose limiting with broad action GABA modulators such as benzodiazepines, the challenge is to develop drugs that are selective for the nature of the GABAergic dysfunction seen in schizophrenia. Recent interest has focussed on the alpha 5 subtype of the GABA(A) receptor, which shows high expression in the hippocampus (Stefanits et al., 2018) and is predominantly involved in generating a tonic inhibitory current (Brickley and Mody, 2012; Martin et al., 2010) to regulate the excitability of pyramidal neurons (Glykys and Mody, 2006, 2007; Pavlov et al., 2009) and decrease network excitability (Stokes et al., 2014). Mice deficient in alpha 5 $GABA_A$Rs show reduced tonic inhibition resulting in hippocampus hyperexcitability (Glykys et al., 2008; Glykys and Mody, 2006), consistent with findings in schizophrenia and people at risk of developing schizophrenia (Bossong et al., 2018; Weiss et al., 2003). This suggests that alpha 5 subtype selective GABA agonists might be effective for schizophrenia. A positive allosteric modulator (PAM) that acts at alpha 5 subtypes of the GABA receptor has been tested in the methylazoxymethanol acetate (MAM) neurodevelopmental model of schizophrenia (Gill et al., 2011). This showed the alpha 5 PAM reduced evoked responses in hippocampal neurons from both control and MAM animals and reduced the activity of dopamine neurons in the MAM animals to control levels. Modulation of potassium channels selectively expressed on parvalbumin positive interneurons is another approach for targeted GABA-ergic augmentation which shows promise in preclinical studies (Boddum et al., 2017; Rosato-Siri et al., 2015). However, whilst promising, these approaches have yet to be tested in patients (Girgis et al., 2018).

6.2. The cannabinoid system and beyond

The cannabinoid system is of interest as cannabis use has been associated with increased risk of developing psychosis primarily due to the psychoactive component tetrahydrocannabinol (THC) (Lowe et al., 2018; Murray et al., 2007). Endocannabinoids, such as anandamide (*N*-arachidonoylethanolamine; AEA) and 2-arachidonoylglycerol (2-AG), are synthesized and released from postsynaptic neurons but act predominantly at presynaptic CB1 receptors in a retrograde fashion (Wilson and Nicoll, 2001). Activation of CB1 receptors inhibits presynaptic neurotransmitter release, including from the dopamine system (Chevaleyre et al., 2006). The dysregulation of the endocannabinoid system as observed by the lower levels of AEA in cannabis users has led to the hypothesis that downregulation of the AEA signalling can facilitate psychosis as low levels would not inhibit excess dopamine release in synapses (Giuffrida et al., 2004; Leweke et al., 2012). Cannabidiol (CBD), a phyotocannabinoid from the cannabis plant, may inhibit fatty acid amid hydrolase (FAAH) the enzyme that breaks down AEA, and so could potentially boost CB1 mediated feedback on dopamine neurons (Leweke et al., 2012). CBD is currently being investigated for its antipsychotic activity and initial reports are promising (Leweke et al., 2012; McGuire et al., 2018).

Finally, recent findings have provided new insights into the localisation of striatal dopamine dysregulation (Howes et al., 2009c; Kegeles et al., 2010). Meta-analysis of these shows that the degree of striatal dopamine dysfunction in schizophrenia is not uniform, with the elevation in dopamine synthesis capacity and synaptic dopamine levels in schizophrenia predominantly localised to the dorsal, rather than ventral, striatum, and particularly in the part of the dorsal striatum that receives projections from associative cortical regions such as the dorsolateral prefrontal cortex (McCutcheon et al., 2017). This suggests that targeting the regulation of dopamine function in this part of the dorsal striatum, or, alternatively, regionally selective dopamine receptor blockade, would be more effective for psychosis and reduce the risk of side-effects (McCutcheon et al., 2019). Dopamine receptors show differences in their density across the striatum, and the organisation of regulatory inputs also varies across the striatum, suggesting that regionally selective modulation of the dopamine function could be possible (Weinstein et al., 2017). For example agents such as the muscarinic M1/M4 positive allosteric modulator xanomeline (Shekhar et al., 2008) could specifically inhibit dorsal striatum dopamine transmission via muscarinic modulation (Fig. 5) (McCutcheon et al., 2019).

7. Treating the negative and cognitive symptoms of schizophrenia

The negative symptoms of schizophrenia such as avolition/apathy and diminished expression (Kaiser et al., 2017) are a long term cause of health burden in at least 60% of patients with schizophrenia (Stiekema et al., 2018). Negative symptoms show some improvement when antipsychotics are compared with placebo in clinical trials (Leucht et al., 2017). However, the changes are relatively modest and may not be clinically significant (Fusar-Poli et al., 2015), though such studies may mask sub-groups of patients with negative symptoms who do improve (Stiekema et al., 2018). Negative symptoms have been hypothesised to be due to hypofrontality and frontal hypodopaminergia, in part based on the finding that frontal lobe lesions can cause similar behavioural changes to negative symptoms (Davis et al., 1991), but also from numerous neuroimaging studies linking deceased frontal activation in patients with schizophrenia and higher negative symptom scores (Andreasen et al., 1992; Potkin et al., 2002; Schroder et al., 1996; Wolkin et al., 1992). Hypoactivation in response to reward-indicating cues in the left ventral striatum also correlates with higher negative symptom scores in patients with schizophrenia (Radua et al., 2015) and may be specific to the apathy rather than diminished expression dimension of negative symptoms (Kirschner et al., 2015). However, it is now thought that multiple neurotransmitter systems underlie the

cognitive and negative symptoms of schizophrenia (Galderisi et al., 2015; Howes and Kapur, 2009), and in addition, antipsychotics may contribute to secondary negative symptoms, as discussed above.

Up to 80% of patients with schizophrenia have some form of cognitive impairment (Reichenberg et al., 2009), which may predate the onset of schizophrenia (Bora and Murray, 2014) and is associated with poor outcomes (Green, 2016). Antipsychotics improve cognitive functioning in first episode and chronic patients when cognitive testing is repeated over time, but there seems to be little difference between agents and some patients show limited improvement (Davidson et al., 2009; Keefe et al., 2007; Mishara and Goldberg, 2004; Nielsen et al., 2015; Woodward et al., 2005). Molecular imaging studies have linked dopaminergic function to performance on cognitive tasks. In healthy controls dopamine release in frontotemporal dopaminergic circuits correlates positively with working memory performance (Aalto et al., 2005) and drug-free patients with schizophrenia appear to have reduced dopamine release in the anterior cingulate cortex during executive function tasks compared with healthy controls (Rao et al., 2018; Slifstein et al., 2015). Veselinovic et al. (2018) found that executive performance (as measured by the trail-making task) is linked to striatal dopamine D2/3 receptor availability in patients with schizophrenia but not controls. Functional neuroimaging studies find that patients with schizophrenia show reduced neural activation in the dorsolateral prefrontal cortex, anterior cingulate cortex and the thalamus (Minzenberg et al., 2009), regions which are thought to be critical to executive and cognitive functions, during cognitive tasks. Moreover, altered cortical function is linked to striatal dopamine abnormalities in schizophrenia and at-risk populations (Bertolino et al., 2006; Fusar-Poli et al., 2011; Jauhar et al., 2018; Meyer-Lindenberg et al., 2005), suggesting cortical dysfunction could be linked to striatal dopamine abnormalities. This is consistent with theories that striatal dopamine dysfunction is the consequence of cortical dysregulation, and highlights that treating the latter might address both cognitive impairments and psychotic symptoms.

Several initiatives have been developed to address the lack of effective treatments for the cognitive symptoms of schizophrenia. The National Institute of Mental Health (NIMH) sponsored Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (Nuechterlein et al., 2004) identified a number of potential drug targets, that include α7-Nicotinic receptor agonists, dopamine D1 receptor agonists and AMPA glutamatergic receptor agonists amongst others (Marder, 2006) which will be discussed further. Alpha7 nicotinic receptor agonists have been developed to treat cognitive symptoms, due to the finding that nicotine appears to improve attention in some patients with schizophrenia (Harris et al., 2004). Yet such agents have not proved efficacious in phase 3 clinical trials to date, which notwithstanding the general challenges of replicating positive findings in phase 3 trials, may be related to acute receptor desensitisation during trial treatment and the inclusion of trial subjects who smoke and therefore have chronic receptor desensitisation (Tregellas and Wylie, 2018). Dopamine agonists such as atomoxetine, or psychostimulants such as lisdexamphetamine have been trialled in treating cognitive and negative symptoms in schizophrenia (Solmi et al., 2018a). However, despite benefits for negative symptoms in early open-label studies (Lasser et al., 2013), a recent meta-analysis of stimulant treatments in schizophrenia to date found no clear evidence of benefit (Solmi et al., 2018a). Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptors are a class of ionotropic glutamate receptors (Traynelis et al., 2010) that share a similar architecture to NMDA receptors (composed of glutamate receptor subunits GluA1-GluA4 vs. GluN1, GluN2A–GluN2D, GluN3A, and GluN3B in the case of NMDA) (Herguedas et al., 2016). AMPA receptors mediate excitatory signally within the brain (Benke et al., 1998). For example, in response to glutamate, post-synaptic AMPA receptors are involved in rapid depolarisation and changes in long-term potentiation and gene expression which are thought to be critical to synaptic plasticity and learning (Bliss and Collingridge, 1993; Malinow and Malenka, 2002). AMPA receptor modulators are under investigation as an indirect mechanism for treating the glutamatergic dysfunction found in schizophrenia (Gray and Roth, 2007). However, post-mortem studies measuring AMPA receptors in schizophrenia have been inconclusive, indicating it is not clear what role they play in the pathophysiology of the disorder (Tani and Suzuki, 2017), and so far, no AMPA agent has been successful in improving cognition in patients with schizophrenia in trials (Goff et al., 2007; Ward et al., 2015).

Partly in response to the lack of progress in the development of treatments for the negative and cognitive symptoms of schizophrenia, the NIMH are building a set of Research Domain Criteria (RDoc) with the aim of better understanding underlying disease constructs in schizophrenia, such as positive and negative valence systems and cognitive systems (Morris and Cuthbert, 2012).

8. Transdiagnostic considerations

There is considerable interest in whether the neurobiological abnormalities underlying the psychotic symptoms of schizophrenia are unique to the disorder or if there is a common mechanism that underlies psychosis across disorders such as bipolar and schizophrenia. There is some evidence from neuroimaging studies that dopamine abnormalities are present in bipolar disorder, in particular patients with mania show increases in dopamine D2/3 receptor availability and appear to have hyper-responsive reward systems in the ventral striatum (Ashok et al., 2017). Moreover, dopamine synthesis capacity appears to be elevated in patients with bipolar psychosis to a similar degree to that seen in schizophrenia (Jauhar et al., 2017a). More studies that compare aspects of dopamine function across psychotic disorders would help determine if there are differences in the nature of the dopaminergic dysfunction between disorders. Notwithstanding the limited comparative evidence on dopamine function, another line of evidence for a common mechanism comes from clinical trials. These indicate that both first- and second-generation antipsychotics are effective in treating acute mania in bipolar disorder, with effect sizes similar to those seen in schizophrenia (Cipriani et al., 2011). Furthermore, antipsychotics are being explored as treatments for maintenance therapy in bipolar disorder (Jauhar and Young, 2019; Prajapati et al., 2018). Antipsychotic drugs are also effective for depression, particularly psychotic depression (Farahani and Correll, 2012). However, it remains to be determined if the therapeutic effects of antipsychotic drugs in bipolar disorder or depression are mediated by D2 occupancy, although the relationship between D2 occupancy and extra-pyramidal side-effects in bipolar seems to be the same as that seen in schizophrenia (Attarbaschi et al., 2007).

9. The role of antipsychotic polypharmacy

A recent study by Tiihonen et al. (2019) provides real-world evidence for the use of some antipsychotics in combination to reduce the risk of rehospitalisation in patients with schizophrenia. Clozapine in combination with aripiprazole was found to be associated with the lowest rehospitalisation risk and associated with better outcomes than clozapine monotherapy, which was the most effective monotherapy. This could be due to one of three mechanisms: polypharmacy leads to greater dopamine D2 occupancy and blockade which increases efficacy; or a reduction in side effects which increases tolerability, for example reduced weight gain when aripiprazole is added to clozapine and reduced prolactin levels when aripiprazole is added to other dopamine D2 antagonists (Galling et al., 2017); or finally, the addition of a second agent induces beneficial effects via actions at other receptors. Of course, these mechanisms are not mutually exclusive, and further work is required to identify which underlie the potential real-world benefits of polypharmacy.

10. Beyond dopamine: inflammation and immune modifiers

Over the last decade or so, over two hundred compounds for targets other than dopamine D2/3 receptors have been evaluated for schizophrenia but, to date, none have made it to market (Millan et al., 2016). Clearly developing an antipsychotic that does not act on the dopamine system is not easy. Notwithstanding this, the immune system has emerged as a major therapeutic target, not least because recent meta-analyses indicate that immune alterations are evident from the onset of illness and are more marked than many CNS abnormalities (Pillinger et al., 2018). Theories that schizophrenia has an immune pathoetiology date back decades (Ganguli et al., 1994; Muller and Ackenheil, 1998) and several different anti-inflammatory treatments have been evaluated in the treatment of schizophrenia. The addition of non-steroidal anti-inflammatories (NSAIDs) such as aspirin or celoxcib to antipsychotics has shown improvements in positive and negative symptoms, but effect sizes were relatively modest and may lack clinical significance (Nitta et al., 2013; Sommer et al., 2013). Adjunctive minocycline, an antibiotic with anti-inflammatory actions, has also been trialled but the results have been inconsistent (Chaudhry et al., 2012).

The modest effect sizes for NSAIDs and inconsistency in findings for minocycline may be because these agents are not specific enough to the immune pathophysiology found in the brain (Deakin et al., 2018). With respect to this, several lines of evidence has suggested that microglia, the main immune cell in the brain, could play a central role in the pathophysiology of schizophrenia (Howes and McCutcheon, 2017; Miller and Goldsmith, 2017; Sekar et al., 2016). Firstly, one of the most significant genome wide associations with schizophrenia is to a genetic variant that preclinical models suggest alters microglial mediated synaptic pruning (Sekar et al., 2016) and stress, a major environmental risk factor for schizophrenia, increases microglial markers in brain regions relevant to the pathophysiology of schizophrenia such as the prefrontal cortex and hippocampus (Calcia et al., 2016). Secondly, post-mortem studies show evidence for increased microglial markers in brains of patients with schizophrenia relative to controls with moderate-large effect sizes on meta-analysis (Trépanier et al., 2016). Thirdly, molecular imaging using PET tracers for the translocator specific protein, which is expressed by microglia, has been used to investigate if there are alterations in schizophrenia in vivo, and linked to symptom severity in some cases (Bloomfield et al., 2016; Holmes et al., 2016). Alterations are seen in cortex with small to moderate effect sizes seen on meta-analysis (Plaven-Sigray et al., 2018; Reis Marques et al., 2018) although the direction seems to depend on the methodology used (Reis Marques et al., 2018). Finally, microglia-like cells derived from patients with schizophrenia show increased synaptic elimination in in vitro models (Sellgren et al., 2019), suggesting aberrant microglia mediated synaptic pruning might explain the cortical synaptic density reductions reported post-mortem in schizophrenia (Osimo et al., 2018), and that targeting microglia might prevent structural brain changes seen in schizophrenia (Howes and McCutcheon, 2017). Taken together, these findings suggest microglia as a potential therapeutic target which, by preventing aberrant synaptic pruning could be disease modifying. However, microglia play important physiological roles and have both pro and anti-inflammatory effects, so modulation of their function needs to be approached cautiously, and the phase of illness may be critical, particularly if treatment is to prevent aberrant synaptic pruning that occurs early in the illness. The acid test of the therapeutic potential of targeting microglia is, of course, a clinical trial. Several monoclonal antibody trials targeting microglia or cytokines linked to them are currently underway (Girgis et al., 2018; Miller et al., 2016), and should read out in the next few years.

11. Conclusions

All drugs currently licensed to treat schizophrenia are dopamine D2/3 blockers, despite past efforts to develop alternative approaches (Millan et al., 2016). Moreover, molecular imaging studies have shown that D2/3 receptor blockade is necessary for the therapeutic action of current drugs, although it does not guarantee response. Despite this, studies of the dopamine system in patients with schizophrenia have shown that there is not a major alteration in dopamine D2/3 receptors in schizophrenia. Rather the major alteration is presynaptic, characterised by increased striatal dopamine synthesis and release capacity predominantly in dorsal regions of the striatum linked to psychosis, and potentially reduced dopamine release in cortical regions underlying cognitive impairments. These findings explain why post-synaptic dopamine receptor blockade works to reduce the positive symptoms of schizophrenia. They also highlight that current drugs acts downstream of the underlying dopamine abnormalities and block physiological signalling that is needed for normal brain function as well as. Imaging studies have shown that for most agents, whilst substantial dopamine D2/3 receptor blockade is needed for a therapeutic effect, dopamine D2/3 receptor blockade also contributes to some side-effects, particularly motor side-effects and prolactin elevation.

Current agents also have many off-target effects on other receptors, such as serotonin, histamine, muscarinic and alpha-adrenergic receptors. Our review highlights that there is a paucity of in vivo studies of these systems in schizophrenia, and a need for in vivo studies in patients free from the confound of antipsychotic treatment. Notwithstanding this limitation, the neurobiological evidence available to date does not clearly implicate these systems in the pathophysiology of psychosis, nor does the in vivo evidence support a major role for these receptors in mediating the antipsychotic effect of current drugs. This reinforces the centrality of dopamine receptor blockade for the action of antipsychotics. However, our review does highlight how many of the common side-effects of antipsychotics, such as sedation and weight gain, can be understood in terms of these off-target effects. Moreover, it shows that particular side-effects are hard to avoid given the pharmacology of some drugs and the need to block dopamine receptors adequately. These findings have important implications for the choice of current drugs to minimise side-effects. They also have implications for the development of new drugs, indicating that the field should pursue strategies that are more specific to the nature of the dopamine dysfunction in the disorder to minimise side-effects and maximise clinical response. We consider several strategies to do this through reducing dopamine synthesis, targeting autoregulation, or modulating the upstream control of dopamine neurons via the glutamate or GABAergic systems. The negative and cognitive symptoms of schizophrenia remain a challenge to treat within the limitations of current medications and despite several promising leads in early phase studies, we are yet to find agents that significantly improve such symptoms. Further work in this area is essential and on-going.

Finally, our review identifies the emerging neurobiological evidence showing the potential of targeting microglial function as an example of a completely non-dopaminergic approach. Whilst this looks promising, a key lesson from the findings on dopamine dysfunction in schizophrenia is that it is more complex than was initially thought. Moreover, there are key aspects even of the dopamine dysfunction in schizophrenia that are not understood; perhaps most critically if cortical hypodopaminergia is present at the same time as striatal hyperdopaminergia, and whether the mechanisms underlying these are distinct. This highlights the need for more fundamental studies of the nature of alterations in the dopamine, immune and other systems in schizophrenia to guide drug development.

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