Pharmacological treatment of schizophrenia – a review of progress

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Since much of our knowledge about the neurobiology of schizophrenia derives from the initial discovery that chlorpromazine was effective in treating psychosis, pharmacological research has mostly concentrated on dopamine-blocking agents. Here, the authors discuss the situation where there is no single pharmacological agent on the horizon that could serve as the ‘holy grail’ to address the full range of symptoms of schizophrenia and what the immediate future holds with the widespread use of polypharmacy.

Schizophrenia is a syndromic condition, characterised by a set of signs and symptoms, which remain largely unchanged since the inception of the term by Swiss psychiatrist Eugene Bleuler over 100 years ago.

Individuals suffering with schizophrenia typically present with discrete episodes of psychotic symptoms, generally disturbances of thought and hallucinatory experiences, which are collectively called positive symptoms; there are also more pervasive cognitive, affective and interpersonal deficits, which have devastating effects on quality of life. These include apathy, lack of will and motivation, reduced expression of emotion and social withdrawal, collectively called negative symptoms.

A systematic review of meta-analyses of international epidemiological data finds a mean point prevalence of 4.5 per 1000 and an all-cause standard mortality ratio of 2.7,1 clearly identifying schizophrenia as a major risk factor for excess mortality. The course of schizophrenia tends to be chronic, with only around 1.4% of treated patients attaining a satisfactory recovery state per year.2

Since the serendipitous discovery of antipsychotic drugs in the 1950s and their overwhelming success in treating psychosis, there has been a shift from the predominant psychoanalytic approach of the time towards trying to understand the biological basis of this puzzling disorder. As of March 2016 a PubMed (www.ncbi.nlm.nih.gov/pubmed) search for ‘pathogenesis of schizophrenia’ yielded more than 39 000 papers. Despite many decades of intense research, diagnosis is still based exclusively on clinical presentation and there is still no set of valid and reliable biomarkers that can aid with identifying individuals at risk or cases of schizophrenia.3

Development and influence of antipsychotics

The story of antipsychotic medication (for a review see Shen4) begins with the founding of the English textile dye industry after the serendipitous synthesis of the purple dye mauve by W.H. Perking in 1853. Shortly after, the phenothiazine dye methylene blue was synthesised. In 1891, German bacteriologist Paul Ehrlich discovered that synthetic dyes possessed antimicrobial properties and, in particular, methylene blue had antimalarial effects. This led to failed attempts to chemically modify methylene blue in order to produce a clinically useful drug. During the Second World War, the capture of important quinine-producing regions of southeast Asia by the Japanese reignited the interest in developing synthetic antimalarial agents using the phenothiazine ring as a base structure. Fortuitously, researchers at the Rhône-Poulenc Laboratories in France started testing aminoalkyl phenothiazines for antihistamine properties, leading to the discovery of promethazine. This sparked a new era of research into phenothiazine derivatives, used perioperatively during general anaesthesia. This effort led to the discovery of chlorpromazine in 1950, which proved to be an effective antiemetic and sedative without impairing consciousness. In 1952 chlorpromazine was released under the commercial name Largactil. Due to its dampening effects on behaviour, cognition and movement the term ‘neuroleptic’ was coined, now largely replaced by the term antipsychotic. By 1960 chlorpromazine had revolutionised the treatment of schizophrenia, contributing to the abandonment of older unproven and ineffective treatments such as insulin comas, cold hibernation and lobotomies, and aiding the deinstitutionalisation of patients. This great success spurred further research into the development of other agents with similar properties. This effort resulted in the commercialisation of more than 40 first-generation or ‘typical’ antipsychotics with small variations in pharmacological and side-effect profiles.

In 1960 the dibenzodiazepine agent clozapine was synthesised.5 Clozapine is a second-generation agent, which, unlike all other antipsychotics of the era, did not appear to cause debilitating motor side-effects. Nonetheless, it was quickly withdrawn from the market...
due to reports of potentially fatal agranulocytosis – a catastrophic reduction in the number of leukocytes. It returned to prominence in 1988 following the encouraging results of a multicentre clinical trial showing significantly superior efficacy to chlorpromazine in treatment-resistant schizophrenia. This newly found success fuelled research into second-generation antipsychotics, which resulted in agents with good antipsychotic efficacy but with significantly less propensity to cause movement disorders.

For many years the mechanism of action of antipsychotics was unknown and they were being used indiscriminately in most psychiatric disorders under the terms ‘major tranquilisers’ and ‘neuroleptics’. The antidopaminergic theory of action of neuroleptics as proposed by Van Rossum (1966) built on earlier work by Carlsson and Lindqvist (1963) who discovered that chlorpromazine and haloperidol raised catecholamine metabolites in the mouse brain, suggesting an indirect action of antipsychotics, possibly via a dopamine receptor, and an ability of the central nervous system to upregulate the production of catecholamines in response to blockade of their receptors. It was already known that the alkaloid reserpine exerted its antipsychotic properties by blocking monoamine transport into the presynaptic vesicles thus exposing them to degradation by the monoamine oxidase enzymes, therefore depleting their levels. It is important to note that at the time there was a strong debate around the nature of signalling in the nervous system, with fierce arguments between proponents of electrical versus chemical transmission; also, dopamine was considered a molecule of limited significance.

Investigations of the actions of neuroleptics and reserpine, together with observations that amphetamines and L-DOPA can induce psychotic symptoms, led to the dopamine hypothesis of schizophrenia proposed by Solomon Snyder (1976). The original hypothesis postulated that a hyperactive dopaminergic system lies at the core of pathophysiology of schizophrenia. This theory had several limitations: it did not provide a satisfactory explanation for the broad and heterogeneous spectrum of symptoms, there was no integration with other neurotransmitter systems and there was no connection to the heritability of the disorder. In the following years it became apparent that the original theory was not consistent with more recent data from postmortem, neuroimaging and animal studies and that simple hyperdopaminergia couldn’t tell the full story. Davis et al. (1991) reviewed the available data and reformulated the dopamine hypothesis in terms of differential dopamine activity in parts of the brain; they theorised that negative symptoms constitute a hypo-function of dopamine in prefrontal areas and positive symptoms can be explained via hyperfunction of the mesolimbic dopamine system, particularly at the level of the striatum. The evidence for such abnormalities was mostly indirect, deriving from prefrontal lesion studies, Positron emission tomography (PET) of well and affected people, and animal model studies. Subsequent reviews of neuroimaging research showed that reduced dopamine activity in the prefrontal cortex was not a consistent finding and probably depended on research methodology. However, data from molecular imaging techniques reinforced the idea that dopamine is a protagonist in the pathophysiology of schizophrenia. This evidence localises aberrant dopamine function at the level of the striatum where there appears to be increased presynaptic production, storage and release of dopamine. Modern theories postulate that psychotic symptoms are associated with an aberrant activation of the dopaminergic system linked to reward, which tends to fire in response to internal rather than external events, therefore inducing a state in which patients are not able to properly appraise real stimuli. According to this theory, antipsychotics are thought to act by indiscriminately deactivating the salience and reward system and hence producing a relief from positive symptoms.

**Neurobiological theories**

The efficacy of both first- and second-generation antipsychotic drugs is thought to relate directly to dopamine-2 (D2) receptor antagonism. This property is also responsible for the side-effects of abnormal movements (pseudo-parkinsonism, dystonia, tardive dyskinesia) and hyperprolactinaemia. Antipsychotics antagonise other dopamine receptors apart from D2, however their role in the pathogenesis of schizophrenia is not clear.

A few years after the conception of the dopamine theory, its initial proponents, Snyder and Carlsson, criticised the simple single neurotransmitter model. Other neurotransmitters and receptor systems have been implicated in the pathophysiology of schizophrenia, such as glutamate, glycine and noradrenaline.

**N-methyl-D-aspartate (NMDA) receptor antagonists**, such as the dissociative agents phencyclidine and ketamine, can produce the full range of positive and negative symptoms that one sees in schizophrenia. This observation led to the NMDA receptor hypofunction model, which postulates that reduced NMDA receptor function on inhibitory GABAergic interneurons reduce their firing rate leading to disinhibition of glutamatergic projection neurons. Increased neuronal excitation from glutamate can have neurotoxic effects leading to neuronal degeneration in animal models and could provide an explanation for the observed reduction in brain volume observed in schizophrenia. Molecular neuroimaging studies give support to this hypothesis as...
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it is not clear how this happens and what role the difference suggests that there may be a role for noradrenergic neurotransmission with little to no affinity for serotonin 5-HT2C, higher doses exhibits dopamine D2 receptor antagonism, which at lower doses for the treatment of sleep difficulties and mood disturbances and at higher doses, where D2 antagonism is more prominent, for both mood and psychotic symptoms. Furthermore, its low affinity for 5-HT2C, H1 and α1A receptors ought to minimise side-effects associated with atypical antipsychotics such as weight gain, sedation and orthostatic hypotension. Furthermore, at therapeutic doses it increases phosphorylation of the GluN2B subunits of the NMDA receptor, indirectly leading to enhanced glutamatergic transmission in the mesolimbic pathway. Although previous attempts to solely target the glutamatergic system were not as fruitful as expected, there is a well-identified link between glutamate and dopamine neurotransmission in schizophrenia and the combination of glutamatergic together with antidopaminergic action may prove more effective in practice. A phase II 4-week randomised, double-blind, controlled trial showed both statistically and clinically significant improvement in schizophrenia symptoms compared with placebo and comparable efficacy to risperidone. In the same study ITI-007 fared better compared with risperidone for negative and extrapyramidal symptoms. As of June 2015 Intra Cellular Therapies was recruiting subjects for a 6-week phase III controlled trial to further assess its efficacy (NCT02469155).

RP5063 is a dopamine/serotonin system stabiliser, which completed a phase II clinical trial with promising results. At all therapeutic doses it demonstrated superior efficacy compared with aripiprazole, with a side-effect profile comparable with placebo. The developing company hopes that, due to its unique receptor profile, RP5063 will prove effective for the treatment of anxiety-depressive and cognitive symptoms in schizophrenia and is currently developing a multicentre phase III clinical trial.

Serotonin receptor ligands are in development for many different conditions. 5-HT2A antagonism is one of the properties that make an antipsychotic ‘atypical’ and it is thought that a high ratio of 5-HT2A to dopamine receptor binding results in fewer extrapyramidal side-effects. Pimavanserin (ACP-103), a selective serotonin inverse agonist, was compared with placebo in co-therapy with either risperidone or haloperidol in patients with schizophrenia in a phase II clinical trial (NCT00361166). The sponsoring company (Acadia Pharmaceuticals) reported superior efficacy and fewer side-effects for the combination of pimavanserin with an antipsychotic. The same company is currently recruiting for a phase II trial to test pimavanserin for the treatment of Alzheimer’s disease psychosis (NCT02035553), with no further registered trials for schizophrenia. A 5-HT2C agonist under the name loraserin was approved by the FDA in 2012 for the treatment of obesity. Similar agents could help tackle the...
<table>
<thead>
<tr>
<th>Name</th>
<th>Sponsor</th>
<th>Mechanism of action</th>
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<td>ITI-007&lt;sup&gt;25&lt;/sup&gt;</td>
<td>IntraCellular Therapies</td>
<td>Presynaptic partial D2 agonist, postsynaptic D2 antagonist, 5-HT2A antagonist, SERT antagonism, increased GluN2B phosphorylation</td>
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<td>NCT02469155</td>
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<td>RP5063&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Reviva Pharmaceuticals</td>
<td>Partial D2, D3, D4 agonist partial 5-HT1A and 5-HT2A agonist 5-HT6 and 5-HT7 antagonist</td>
<td>Phase III completed</td>
<td>NCT01490086</td>
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<td>Bexarotene (LGD1069)&lt;sup&gt;47&lt;/sup&gt;</td>
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<td>Olanzapine / Samidorphan (ALKS-3831)&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Alkermes</td>
<td>Combination of a second-generation antipsychotic with a mu-opioid receptor antagonist</td>
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<td>NCT02694328 NCT02634346</td>
<td>Positive symptoms and hyperphagia associated with olanzapine</td>
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<td>ACP-103&lt;sup&gt;50&lt;/sup&gt; (Pimavanserin)</td>
<td>Acadia Pharmaceuticals</td>
<td>5-HT2A inverse agonist</td>
<td>Phase II completed</td>
<td>NCT00361166</td>
<td>Psychosis</td>
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<td>AVN-211&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Avineuro Pharmaceuticals</td>
<td>5-HT6 antagonist</td>
<td>Phase II completed</td>
<td>?</td>
<td>Cognitive symptoms</td>
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<tr>
<td>Ondansetron</td>
<td>University of Colorado</td>
<td>5-HT3 antagonist</td>
<td>?</td>
<td>NCT00149734</td>
<td>Adjunct treatment</td>
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<td>JNJ-40411813&lt;sup&gt;52&lt;/sup&gt; (ADX-71149)</td>
<td>Janssen</td>
<td>mGlu2 positive allosteric modulator, 5-HT2A antagonist</td>
<td>Phase II completed</td>
<td>NCT01323205</td>
<td>Negative symptoms</td>
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<td>Bitopertin (RG1678)</td>
<td>Hoffman-La Roche</td>
<td>GlyT1 inhibitor</td>
<td>Phase III completed</td>
<td>NCT01234779 NCT01192906 NCT01235559 NCT01235585 NCT01192906</td>
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<td>GlyT1 inhibitor</td>
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<td>α7-nACh receptor agonist</td>
<td>Phase II</td>
<td>NCT01163227 NCT01730768 NCT01678755 NCT01655680</td>
<td>Cognitive symptoms Adjunct treatment</td>
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<td>EVP-6124 (Encenicline)</td>
<td>EnVivo Pharmaceuticals</td>
<td>α7-nACh receptor agonist</td>
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<td>NCT01714713 NCT00968851 NCT01714661 NCT01716975</td>
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<td>OMS643762 OMS824&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Omeros</td>
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<td>Phase II completed</td>
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<td>Oxytocin (Syntocinon)&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Various (mainly academic sponsors)</td>
<td>Oxytocin nasal spray</td>
<td>Numerous studies Phase 0-IV</td>
<td>NCT01614093 NCT00884897 and others</td>
<td>Interpersonal deficits Satiety</td>
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<td>Nitroprusside</td>
<td>New York University School of Medicine</td>
<td>NO-releasing drug</td>
<td>Phase II recruiting</td>
<td>NCT02695589</td>
<td>Positive, negative and cognitive symptoms</td>
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Table 1. Update on the clinical trials for the pharmacological treatment of schizophrenia
increased appetite and weight gain caused by existing antipsychotics, but to our knowledge no phase II or III trials are being conducted. 5-HT3 antagonists such as ondansetron are widely used for the treatment of nausea and are thought to contribute in treating negative symptoms when used together with current antipsychotics.29 The same studies have also shown reduced incidence of extrapyramidal side-effects. Despite preliminary promising results, a double-blind, placebo controlled clinical trial (NCT00149734) testing the efficacy of ondansetron as adjunct therapy does not have publicly available results. 5-HT6 antagonism has shown some pro-cognitive effects in animal models.30 Several 5-HT6 antagonists are currently undergoing clinical trials for Alzheimer’s disease. The highly selective 5-HT6 receptor antagonist AVN-211 was trialled as adjunct treatment to an atypical antipsychotic in a phase II clinical trial showing superiority to placebo.31 From a theoretical point of view, agents that stimulate the NMDA receptor should provide relief or, at least, protect from negative symptoms and possibly from cognitive decline. There has been a significant financial investment in developing a glutamatergic antipsychotic and several agents have been trialled with limited success (for review of such treatments see Tandon, et al.32). The phase III clinical trial of pomaglumetad methionil, a glutamate receptor 2 and 3 agonist, was stopped following an interim ‘futility’ analysis which showed that it would not meet the expected efficacy endpoint.33 Despite these setbacks, there is an ongoing effort to develop drugs that target NMDA signalling abnormalities. Reduced activity of group 2 metabotropic glutamate (mGlu2) receptors has been implicated in the pathogenesis of schizophrenia and anxiety disorders,34 possibly by increasing neuronal excitability in the prefrontal cortex and hippocampus. mGlu2 receptor positive allosteric modulators (PAMs) reinforce the response to endogenous glutamate and provide a strategy for increasing mGlu2 receptor activity. JN]-40411813 (ADX-71149) is a mGlu2 PAM which was compared with placebo as adjunct treatment to an antipsychotic in patients with residual positive or negative symptoms (NCT01323205). JN]-40411813 was generally well tolerated and appeared to benefit more those patients that had residual negative symptoms.35 At the moment there are no registered trials for JN]-40411813.

Glycine is an amino acid with inhibitory neurotransmitter properties, which among its other functions is thought to potentiate NMDA function.36 Inhibition of the glycine transporter 1 (GlyT1) protein leads to elevated glycine levels and consequently enhancement of NMDA transmission. Bitopertin is a GlyT1 inhibitor, which has undergone extensive testing in phase II and III trials with unpromising results.37 Currently, Yale University is recruiting subjects with schizophrenia into a phase II clinical trial for the translational optimisation of GlyT1 inhibitor PF-03463275 (NCT01911676) looking at prefrontal cortex function and cognitive measures compared with placebo. Nitrouprusside is a nitric oxide (NO) releasing drug with an interesting link to schizophrenia. Among its other biological functions, NO activates the enzyme guanylyl cyclase, which catalyses the conversion GTP to cGMP, the latter being an important intracellular secondary messenger involved in the regulation of numerous cellular functions. The hypothesis that in schizophrenia there is a dysregulation of the NO-cGMP pathway38 has been supported by recent experimental evidence.39 A randomised, double-blind, placebo controlled trial of slow intravenous infusion of nitrouprusside in patients with an established diagnosis of schizophrenia presenting with an acute psychotic episode showed rapid and persistent improvement in both positive and negative symptoms.39 Currently, the New York School of Medicine is recruiting participants for a phase II clinical trial (NCT02695589) to demonstrate the efficacy of nitrouprusside in treating positive and negative symptoms.

There is a well-established epidemiological link between tobacco smoking and schizophrenia40 and over the years different theories have been proposed to explain this observation. Recent research supports a genetic link between the α7 nicotinic acetylcholine (α7-nACh) receptor and schizophrenia, with patients having reduced expression at the level of their hippocampi.41 Numerous orthosteric and allosteric ligands of the α7-nACh receptor are being actively developed42 for use in schizophrenia and dementia. Unfortunately, the initial enthusiasm was curbed after α7-nACh receptor agonist TC-5619 did not meet the primary and secondary outcomes in a phase IIb trial (NCT01488929) looking at its efficacy for treating negative and cognitive dysfunction symptoms in patients with schizophrenia. There are at least three α7-nACh receptor agonists (ABT-126, AQW051, EVP-6124) undergoing phase II and III clinical trials and their results will determine the future of nicotinic receptor agonism in the treatment of patients with schizophrenia.

Phosphodiesterases (PDEs) are a ubiquitous class of enzymes involved in the metabolism of the intracellular secondary messengers cGMP and cAMP. There are more than 60 distinct PDE isoforms, of which PDE-10A is exclusively found in medium spiny neurones forming the majority neuronal population of the striatum. There is evidence to suggest that PDE-10A regulates nigrostriatal communication,43 which in turn is thought to attenuate the intensity of inputs into the basal ganglia. This pathway is known to play a role in reward attribution, avoidance learning and has been
implicated in the pathogenesis of schizophrenia. D2 receptor transmission requires PDE-10A-dependent cGMP and cAMP signalling, with PDE-10A inhibitors appearing to be more effective at inhibiting dopaminergic basal ganglia circuitry when compared to haloperidol in mice, suggesting that they could be used as alternatives to current dopamine receptor antagonists. In 2014 pharmaceutical company Omeros completed a phase II trial of OMS824 (NCT01952132). However, no results have been published yet.

Bexarotene is a third-generation retinoid acting via activation of the nuclear retinoid X receptors, approved for the treatment of cutaneous T-cell lymphoma and off licence for other types of neoplasms. There is some evidence to suggest that bexarotene clears amyloid plaques in an Alzheimer’s disease mouse model, resulting in the reversal of cognitive and social deficits. Bexarotene as an antipsychotic augmenting agent was compared with placebo in a phase III clinical trial (NCT00535574). It showed significant improvement in positive and negative symptoms with moderate effect size. It was generally well tolerated, however, it caused a significant increase in total cholesterol and thyroxine levels. It is unclear whether there is further research into the compound’s potential uses in schizophrenia.

Oxytocin is a nonapeptide hormone secreted by the pituitary gland. It is physiologically implicated in the lactation reflex and is licensed for labour induction. There has been a surge in trials investigating the purported prosocial effects and empathogenic properties of oxytocin in the treatment of schizophrenia. Preliminary results do not show any significant effect in social interaction or symptom scores when intranasal oxytocin is compared with placebo as adjunct treatment. Despite this, there are currently several active clinical trials looking at the social-cognition-enhancing effects of oxytocin in schizophrenia.

Samidorphan is a mu-opioid receptor antagonist similar in efficacy to naltrexone and is thought to reduce addictive behaviours and, in particular, hyperphagia associated with olanzapine. It is currently being developed as a combined preparation with olanzapine under the name ALKS-3831. A phase II trial comparing ALKS-3831 with a combination of olanzapine and placebo (NCT01909837) was recently completed; however, no results have been published yet. There appears to be further development with two phase III trials under the umbrella of the ENLIGHTEN clinical programme, which is currently recruiting patients with schizophrenia.

**Conclusion**

It should be no surprise that since much of our knowledge about the neurobiology of schizophrenia derives from the initial discovery that chlorpromazine was effective in treating psychosis, pharmacological research has mostly concentrated on dopamine-blocking agents. Currently, all of the licensed medications for schizophrenia have in common the D2-receptor blockade properties with good effect in treating positive symptoms. Dopamine receptor partial agonism, first tried with aripiprazole, has also yielded good results; brexipiprazole and cariprazine, both atypical antipsychotics with D2 partial agonist properties, were approved for the treatment of schizophrenia by the FDA in July and September 2015, respectively. Clozapine is considered the gold standard for treatment-resistant schizophrenia and is more effective in that group of patients compared with other antipsychotics. However, there are currently no licensed drugs that can be used to treat negative and cognitive decline symptoms.

Ongoing research efforts have shown that schizophrenia is much more than the dopaminergic theory, with major neurotransmitter and intracellular messenger systems playing a role. As a consequence, in the last decade there has been a shift towards a much welcomed rational and mechanistic approach to drug development. Considering the devastating impact of schizophrenia, the number of novel antipsychotic agents and adjunctive treatments currently undergoing phase II and III clinical trials (Table 1) is not impressive. This reflects, for some, a ‘crisis’ in developing novel psychiatric drugs. Our review illustrates that the industry appears to recognise the unmet need of addressing the full spectrum of symptoms in schizophrenia. However, the lack of comprehensive, publicly available data makes it difficult to predict the future of pharmacological treatments. On one hand it is encouraging to see that repurposed agents are being explored as adjunctive treatments for negative and cognitive symptoms, on the other it could also be an indication that there is a loss of interest in developing novel agents. At present, there appears to be no single pharmacological agent on the horizon that could serve as the ‘holy grail’ in addressing the full range of symptoms of schizophrenia and at the same time minimise motor, metabolic and cognitive side-effects. It is probable that in the immediate future we will see widespread use of combined treatment with different medications based on the particular symptom profile they address, allowing for a more tailored approach.

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Declaration of interests

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References

News

Action urged to tackle smoking in people with mental health conditions

Action on Smoking and Health (ASH) says ‘urgent action’ is needed to tackle the high smoking rate among people with mental health conditions, according to a new report. http://www.ash.org.uk/stolenyears

With one third of adult tobacco consumed by people with a mental health condition, the organisation says change is needed from all areas of the health and social care system in order to bring the figures down.

People with a mental health condition die on average 10-20 years earlier than the general population, and smoking plays a large role in this says ASH.

The report says there should be better access to medications that will help people give up smoking, improved understanding around electronic cigarettes, and more evidence based services and peer support for people who need them. The report also says prevention is important and people who are at risk of developing a mental health condition should be identified with interventions in place to help prevent them starting to smoke.

ASH is calling for all inpatient and community mental health sites to be smoke-free by 2018, through the implementation of guidance from the National Institute for Health and Care Excellence.

Daclizumab improves cognition

Daclizumab (Zinbryta) improves cognition in patients with Multiple Sclerosis, according to research revealed at the 68th Annual Meeting of the American Academy of Neurology. (Improved cognitive outcomes in relapsing-remitting multiple sclerosis with daclizumab in the phase 3 DECIDE study, 2016)

The data demonstrates daclizumab’s positive effect on processing speed and attention in patients with relapsing-remitting multiple sclerosis (RRMS)

Cognitive impairment is a common symptom of MS affecting 43–70% of patients and causes significant functional disability, as well as decreased quality of life.

Daclizumab is an investigational compound being developed for the treatment of relapsing forms of MS. It is a new form of a humanised monoclonal antibody that selectively binds to the high-affinity interleukin-2 (IL-2) receptor subunit (CD25) that is expressed at high levels on T-cells which become activated in people with MS.

Cognitive decline in MS can involve memory impairment, slowed information-processing speed (including difficulty following conversations or multi-tasking), impaired executive function (including difficulty with organisation or planning), and visual/spatial-processing (including difficulty with right-left orientation or navigation).

Positive recommendation for paliperidone palmitate


Paliperidone palmitate (Xeplion) is an injection administered once every three months, which if approved, would provide the longest dosing interval available for an atypical antipsychotic medication.

The reduced administration required for this drug could improve the lives of people who are struggling with daily or monthly treatments.

‘Poor adherence to treatment is a major trigger for relapse in schizophrenia, therefore the extended duration of treatment possible with paliperidone palmitate may provide helpful support to patients and reduce the need for intervention by their healthcare professional,’ said Leonie Stein, Head of Medical Affairs at Janssen UK.

Paliperidone palmitate is approved for the treatment of schizophrenia in Europe.