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The anticholinergic burden and antipsychotics: Outlook on new drugs in the pipeline

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Abstract

Aims: In addition to their affinity for D2 dopaminergic receptors, antipsychotic drugs prescribed for the treatment of psychotic disorders frequently exhibit anticholinergic side effects. Central M1, M4, or dual M1/M4 receptor agonists are among the current class of mAChR agonists that target psychosis. This article examines the anticholinergic load of antipsychotics and evaluate those currently under development.

Method: A narrative evaluation of the literature was conducted, drawing on data from UPTODATE, BMJ Best Practice, Guidelines, Randomised Clinical Trials, and Studies, as well as current information from other NHS agencies.

Results: There is still disagreement over the best course of action and length of therapy for antipsychotic treatment. We need to promote side-effects data base and digital applications to reduce the cholinergic burden.

Clinical implications: The authors recommends that clinicians understand the anticholinergic burden of medications and the cumulative anticholinergic effects of several medications.

Introduction

Dopaminergic and serotonergic pathways are the primary mechanisms by which first- and second-generation antipsychotics reduce psychotic symptoms such as agitation, hallucinations, and delusions. But they also bind to muscarinic receptors, which can cause digestive problems like dry mouth, constipation, urine retention, blurred vision, and confusion, as well as anticholinergic side effects like memory loss and cognitive decline. These negative effects reduce quality of life, especially in older patients as they raise the risk of dementia, falls, and mortality. In addition to their affinity for D2 dopaminergic receptors, antipsychotic drugs now prescribed for the treatment of psychotic disorders frequently exhibit anticholinergic side effects. Research has repeatedly demonstrated a correlation between cognitive impairment and anticholinergic qualities, often known as anticholinergic load, in individuals diagnosed with schizophrenia [1]. These results add to the body of evidence supporting the hypothesis that patients with psychotic disorders who have altered cholinergic systems also have cognitive impairment.

Drug development aiming at enhancing therapies for mood disorders and schizophrenia has been linked to the pathophysiology of the central cholinergic system [2]. Most of the research on acetylcholine's function and potential for therapy has been directed towards schizophrenia, but it has also been linked to the pathogenesis and treatment of other psychiatric diseases. Given their established functional roles in conscious awareness and aspects of information processing, such as attention, working memory, encoding, memory consolidation, and retrieval, cholinergic deficits in basal forebrain structures and their projections in schizophrenia may be especially relevant to the cognitive dysfunction [3].

The article examines the anticholinergic load of antipsychotics and evaluate those currently under development.

A narrative evaluation of the literature was conducted, drawing on data from UPTODATE, BMJ Best Practice, Guidelines, Randomised Clinical Trials, and Studies, as well as current information from other NHS agencies.

The cholinergic system

The cholinergic system in the human central nervous system is composed of three main parts: (i) projections from the basal forebrain nuclei, which innervate the hippocampus, most cortical regions, and some subcortical nuclei; (ii) the pedunculopontine-lateral dorsal tegmental projections from the brainstem to the thalamus, midbrain, and other brainstem regions; (iii) interneurons in the striatum (most abundant) and the nucleus accumbens [4].

Numerous functions, such as motor control, sleep, cognition, and sensory processing are mediated by the cholinergic system of the human central nervous system. Importantly, the nicotinic and muscarinic receptors are the two receptor families that acetylcholine interacts with to regulate all cholinergic system functions [5].

The central nervous system contains nicotinic receptors, also known as cation-permeable ligand-gated ion channels. They consist of beta (β2-4) and alpha (α1–7 and 9–10) subunits that, when joined can form either heteromeric (α2–6 with β2-4 or α7 with α9 or 10) or homomeric (α7–10) pentameric receptors. These receptors appear to have special characteristics and are named after their constituent subunits [7,8].

The metabotropic class of muscarinic receptors consists of the M1–M5 receptors. M1, 3, and 5 all pair canonically to Gq/11 proteins, which promotes the hydrolysis of inositol phosphate, whereas M2 and 4 couple to Gi/o proteins, which lowers levels of Cyclic Adenosine Monophosphate (cAMP). In the human brain, each of the five receptors has a unique distribution pattern that suggests a different function [9].

The balance between activation of both receptor families ultimately determines the functional result of central cholinergic stimulation.

The effects of anticholinergic activity and cholinergic agonism in Schizophrenia

A detailed analysis of the disruptions to the central cholinergic system has already been published [2,10,11]. The main findings are:

1. A generalised reduction in muscarinic receptor levels in the brains of individuals suffering from schizophrenia.
2. Epibatidine binding has been found to be elevated in individuals with schizophrenia, primarily to the α4β2 nicotinic receptor.
3. The α7 nicotinic receptor, linked to a sensory gating defect in individuals with schizophrenia and other psychiatric disorders, is the most studied nicotinic receptor. It has been shown that hippocampus α7 receptor levels are both unchanged and reduced in tissue from individuals suffering from schizophrenia.

Neuroimaging, post-mortem, clinical and pre-clinical models all point to the involvement of muscarinic receptors in the molecular pathophysiology of schizophrenia. These findings give rise to the theory that muscarinic M1 and/or M4 receptor activation would lessen the intensity of schizophrenia symptoms.

Positive, negative, and cognitive symptoms of the condition can all be lessened in intensity by activating central muscarinic M1 and M4 receptors. It might be argued that the pathophysiology of schizophrenia dysregulates CNS processes, including those of the muscarinic M1 and M4 receptors. Consequently, any medication that targets muscarinic receptors approaches clinical use for the treatment of schizophrenia. This is because there is a subgroup of patients within the syndrome of schizophrenia that have a distinct molecular pathology caused by a marked loss of muscarinic M1 receptors [13,14,33].

Central mAChR agonists have proven to be effective antipsychotics without having the direct antagonistic effects on dopamine receptors. Early attempts to manufacture mAChR agonists targeting psychosis Central M1, M4, or dual M1/M4 receptor agonists are among the current class of mAChR agonists that target psychosis because M1 and M4 receptor subtypes are most strongly connected with targets of antipsychotic action [15].

Scoring systems

Among the several scoring systems, it has been demonstrated that the German Anticholinergic Burden Score and the Anticholinergic Cognitive Burden Scale have the highest levels of validity and reliability. Therefore, we integrated these two scales when creating the ACB calculator. According to a systematic study by Lisibach et al. [16], there is no "gold standard scale for measuring cholinergic burden in a patient," even though the ACB and the GABS were the two scales that emerged from the evaluation with identical highest ratings.

A table was created using the ACB calculator tool (higher score indicates higher cholinergic burden):

ABC score 0	1	2	3
Zuclopenthixol depot Sulpiride Amisulpride Benperidol Flupentixol Flupentixol decanoate Lurasidone Pericyazine Cariprazine Prochlorperazine	Fluphenazine decanoate Paliperidone Aripiprazole Risperidone	Loxapine Pimozide Haloperidol	Trifluoperazine Chlorpromazine Olanzapine Clozapine Quetiapine Perphenazine

Drugs with possible anticholinergic burden score 1.

Drugs with definite anticholinergic burden score 2 or 3.

A score of 3+ is associated with an increased cognitive impairment, impairment, functional impairment, falls, and mortality.

If you cannot find your medication listed in the calculator, you can assume it scores 0.

Muscarinic antagonism and its effect on cognition

Acetylcholine (ACh) and its receptors are part of the muscarinic cholinergic system, which is essential for cognitive functions like memory, learning, and attention. Because the muscarinic cholinergic system modulates attention, learning, and memory, muscarinic antagonism, or inhibiting muscarinic receptors, can affect cognition, especially these processes. Nonselective antagonists, such as scopolamine, can affect memory and spatial navigation, but selective antagonists show different effects on M1 and M2 receptors. Muscarinic antagonism's effect on cognition is important for comprehending and may be treating cognitive impairments in diseases like schizophrenia and Alzheimer's disease [17]. By increasing cholinergic transmission through pharmacological intervention, the cholinergic

strategy to treating AD aims to reverse this decline in cholinergic function.

Acetylcholine's effects on cognition are mediated through the muscarinic M1 receptor. Muscarinic M1 agonists, which directly stimulate this receptor, enhance cognition in animal models and cognitive test scores in Alzheimer's patients. Alternatively, by boosting the central release of acetylcholine, antagonists of central presynaptic M2 receptors enhance cognition. For these strategies to be effective and to prevent cholinergic side effects, strong selectivity for a single muscarinic receptor subtype is necessary [18].

Also, schizophrenia is becoming more common in older adults, and there is heterogeneity in quality of life, overall outcomes, and symptom intensity. While some persons exhibit indicators of shifting symptoms and extended non-remission, many people experience persistent illness remission. In this group, depression is a major cause of death, and although suicide rates are higher than those of age-matched peers, most of the excess mortality is due to natural causes. Cognitive decline and diminished awareness of illness have a substantial impact on functional status and quality of life. Antipsychotics are still a crucial component of the treatment plan, even if elderly patients with chronic illnesses may benefit from a gradual dose reduction. Nonpharmacologic psychosocial therapies and interdisciplinary treatment approaches are crucial adjuncts in the care of older adults with schizophrenia, according to Solomon et al. [19].

Yunusa et al. [20] compared the efficacy, safety, and acceptability of pimavanserin, quetiapine, olanzapine, clozapine, ziprasidone, and risperidone for Parkinson's disease psychosis in individuals with the disease. This was done by a systematic review and a network meta-analysis. Without compromising motor function, clozapine, pimavanserin, and quetiapine dramatically reduced symptoms when compared to a placebo. Comparing quetiapine to a placebo, however, showed a significant impairment in cognition.

Antipsychotics are used to treat older adults' psychosis and agitation brought on by dementia. Typical antipsychotics like haloperidol may slightly improve psychosis when compared to a placebo, but Muhlbauer et al. [21] were uncertain if they improve agitation when compared to a placebo (very low-certainty evidence). These drugs probably increase the risk of somnolence (moderate certainty) and extrapyramidal symptoms (high certainty). Standard antipsychotics may slightly reduce agitation and psychosis in dementia patients, according to some data, the authors concluded. Atypical antipsychotics have relatively little effect on psychosis but a slight favourable effect on agitation in dementia patients.

However, their use has raised concerns over the increased risk of death, fast cognitive decline, and cerebrovascular adverse events. Atypical antipsychotic medications may be linked to a little elevated risk of death when compared to a placebo, according to Schneider and colleagues' findings [22].

All cortical and subcortical areas of the brain are innervated by the main cholinergic routes, which start in the brainstem, striatum, and basal forebrain. Cognitive impairment is frequently linked to anticholinergic load from psychotropic (and nonpsychotropic) medications, with exposure to anticholinergic medications, such as antipsychotics, being linked to a markedly elevated risk of dementia. Even after controlling for variables like drug dosage and the severity of the illness, those with psychosis who have higher anticholinergic load perform worse in a variety of cognitive domains, such as working memory, verbal learning and memory, and attention. This cognitive impairment may be exacerbated by second-generation antipsychotics' inhibition of muscarinic cholinergic receptors. On the other hand, in certain cases, selective muscarinic M1/M4 agonism is linked to better negative (and maybe cognitive) symptoms.

New drugs currently going through clinical trials

Recent clinical trials have shown that axiomers of muscarinic acetylcholine receptors can effectively reduce symptoms related to schizophrenia. Thus, it is plausible that a class of procholinergic antipsychotics may emerge in addition to the usual antidopaminergic antipsychotics. Hypofunctioning muscarinic acetylcholine receptors may be a contributing component in the aetiology of schizophrenia in a subgroup of patients. From this perspective, there are several possible in vivo indicators of muscarinic deficiency and, thus, possible reactions to procholinergic treatments. These indicators include the absence of response to antidopaminergic antipsychotics, specific symptom patterns like visual hallucinations and extreme disarray, antimuscarinic antibody levels, ERP markers like mismatch negativity, and radiotracers [25].

During a roundtable discussion with experts about recent advancements in the treatment of schizophrenia [26], it was determined that there were still unmet needs in several important areas. These included: maximising the use of currently available treatments; effectively treating negative and cognitive symptoms; improving medication adherence; developing novel MOAs; preventing adverse effects related to postsynaptic dopamine blockade; and developing individualised treatment plans. All currently marketed antipsychotics, except for clozapine, work primarily by inhibiting dopamine D2 receptors. Muscarinic receptor agonism, trace amine-associated receptor 1 agonism, serotonin receptor antagonism/inverse agonism, and glutamatergic modulation are agents with unique MOAs that have shown promise in phase 2 and 3 trials.

Xanomeline-trospium, also referred to as KarXT from Karuna Therapeutics, is a muscarinic antagonist and agonist combination that selectively stimulates M1 and M4 receptors, which are involved in psychosis and cognition, while blocking peripheral M2 and M3 receptors, which are primarily responsible for cholinergic side effects.

A larger reduction in the PANSS total score was observed in the phase 2 double-blind study, which lasted for five weeks. However, it was linked to both cholinergic and anticholinergic side effects. To ascertain the effectiveness and safety of xanomeline-trospium in patients with schizophrenia, larger and longer trials are needed. (ClinicalTrials.gov number, supported by Karuna Therapeutics and the Wellcome Trust, NCT03697252.). Brannan et al. [27]. Post-hoc analysis on trial data: Correll et al. [28], Sauder et al. [29], Singh [30], Weiden et al. [31].

Phase 3 trial details taken from the non-peer reviewed developer website (https://investors.karunatx.com/news-releases/news-release-details/karuna-therapeutics-announces-positive-results-phase-3-0) a five-week, double-blind, placebo-controlled study comparing the safety, effectiveness, and tolerability of our primary experimental treatment, KarXT, to a placebo in adults with schizophrenia in the US and Ukraine. The main outcome measure was the difference between KarXT and placebo

at Week 5 in the Positive and Negative Syndrome Scale (PANSS) total score, a scale for assessing the severity of symptoms associated with schizophrenia. Change from baseline in the PANSS positive, PANSS negative, and PANSS negative Marder factor subscale of KarXT compared to placebo at Week 5 were among the predetermined secondary objectives.

256 persons with schizophrenia, ranging in age from 18 to 65, signed up for the trial. At the time of enrolment, the patients were enrolled with a verified diagnosis of schizophrenia and psychotic symptoms.

Since schizophrenia is a syndrome, not every patient with the condition will benefit equally from medications that activate muscarinic M1 and M4 receptors. Treatment non-response, however, might be limited to subgroups within the condition with cortical CHRM1 deficiencies or those with one of the cognitive endophenotypes that might be identified by blood transcriptome alterations. A muscarinic (CHRM) M1 and M4 agonist, KarXT (Xanomeline), underwent successful phase 3 studies [33].

While xanomeline does not inhibit dopamine receptors, it does have antipsychotic qualities and can have cholinergic side effects. The peripheral cholinergic effects of xanomeline are lessened by tros[ium, a peripheral restrained muscarinic receptor antagonist. During a 5-week experiment, xanomeline-trospium produced a higher reduction in the PANSS total score than placebo; nevertheless, it was linked to side effects that were both cholinergic and anticholinergic [27].

It is crucial to recognize that Xanomeline's development was stopped because of serious cholinergic side-effects which made early trials of the medication in dementia unsuccessful [34]. Furthermore, there are currently no active comparator groups in trials assessing Xanomelinetrospium (KarXT) or schizophrenia, such as the EMERGENT trials. This means that the trials mainly evaluate the medication to a placebo, which restricts direct comparisons with other antipsychotics. This indicates that there is little information available regarding KarXT's safety and effectiveness in comparison to other therapies [35].

Ulotaront (SEP-363856) is believed to function as an agonist of serotonin 1A (5-HT1A) receptors as well as Trace Amine-Associated Receptor 1 (TAAR1).

Instead of inhibiting postsynaptic dopamine receptors, activation of TAAR1) receptors dampens presynaptic dopamine release or synthesis, which suppresses dopaminergic neurons in specific brain regions related to psychosis.

Phase 2 RCT: 120 patients, 4 weeks of administration; better than placebo. little adverse consequences [36].

Phase 3: DIAMOND experiment with 900 patients is not yet fully disclosed, but it may not be much better than a placebo, despite the high impact of the placebo! (July 2023 update from Pharmaphorum; https://pharmaphorum.com/news/sumitomos-novel-schizophrenia-drug-flunks-phase-3-test)

Trace Amine-Associated Receptor 1 (TAAR1) has been shown to be a promising therapeutic target for the treatment of schizophrenia [37]. Ulotaront, a TAAR1 agonist, may be useful in treating both positive and negative symptoms and has a distinct adverse effect profile from other antipsychotics. It may also lessen metabolic side effects that are frequently linked to antipsychotics. Clinical investigations on its long-term effectiveness and methods of action, however, are scarce.

Lumateperone: With little side effects, Lumateperone is a serotonin, dopamine, and glutamate modulator that may be used to treat schizophrenia [38]. One important component of all currently approved antipsychotic drugs is dopamine D2 Receptor Occupancy (D2RO). The effectiveness of antipsychotics in conjunction with elevated D2RO is frequently restricted by adverse reactions such hyperprolactinemia and motor impairments. One hour after the treatment, the mean peak dorsal striatal D2RO at 60 mg ITI-007 was 39%. Vital signs, electrocardiograms, and clinical chemistry test results, including prolactin levels, did not exhibit any clinically relevant alterations. The mean scores on motor function assessments showed no motor disruptions with lumateperone medication; there were no reports of adverse events including akathisia or any extrapyramidal motor side effects. This degree of occupancy is lower than that of most other antipsychotic medications at their effective dosages, which probably helps explain lumateperone's favourable safety and tolerability profile and lower risk of hyperprolactinemia and movement problems [39].

Kantrowitz [40] reviewed the literature and emphasised the studies involving roluperidone, pimavanserin, and lumateperone as potential treatments for schizophrenia that target serotonin 5-HT 2A receptors.

Tsapakis and colleagues [41] reviewed ten novel drugs in a systematic review; three of these were approved by the FDA (Olanzapine/Samidorphan combination, Lumateperone, and Pimavanserin), and seven were the subject of clinical trials (Brilaroxazine, Xanomeline/Trospium, combination Emraclidine, Ulotaront, Sodium Benzoate, Luvadaxistat, and Iclepertin). It appears that novel drugs under development for the treatment of schizophrenia function outside of the dopamine system. Subsequent research endeavours must concentrate on the most effective utilisation of current remedies, stressing enhancements in medication compliance because of better side-effect profiles. Such tactics include long acting and simultaneous preparations. Above all, innovative modes of action suggest that future drugs should not only treat positive feelings but also the crippling negative and cognitive symptoms without causing the unfavourable side-effects associated with post-synaptic DA blocking.

A selective positive allosteric modulator of M4 receptors, Emaclidine (CVL-231) increases Acetylcholine (Ach) activity while decreasing dopamine release in the brain.

Phase 1 study: Safe in those in good health

Phase 2 is presently in progress [42].

The therapeutic effects of D2 blocking medications, such as clozapine, can be enhanced by Emraclidine and agonists of M4 muscarinic receptors [43]. Over the course of six weeks, empaclidine improved schizophrenia symptoms without causing extrapyramidal side effects or weight increase. The effect size of the total score on the Positive and Negative Syndrome Scale was considerable for negative symptoms but moderate overall.

A novel atypical antipsychotic called Brexpiprazole is being used to treat schizophrenia and treat major depressive disorder. Brexpiprazole shown comparable effectiveness to aripiprazole and quetiapine, but it also came with a number of side effects, such as somnolence (RR=1.87), weight gain (RR=2.74), and akathisia (RR=1.72) [44].

Conclusion

When compared to a placebo for the prevention of relapse, all antipsychotics have risk ratios of less than 1:0, and nearly all of them have 95% credible intervals excluding no impact. Antipsychotics do not differ much in their efficacy to prevent relapses, and the selection of an antipsychotic for maintenance therapy should mostly be based on its tolerability [45]. Nevertheless, it is possible that drugs with the most cholinomimetic activity such as Clozapine may be the most effective antipsychotics.

By locating the lowest effective dose, reducing side effects, and enhancing adherence, systematic medication management may enhance the risk-benefit ratio of antipsychotics [46].

While recommendations for the ideal range of antipsychotic dosages have been largely consistent, there is still significant disagreement over the best course of action and length of therapy. Guidelines now in use highlight the fact that there isn't a single, universally applicable approach to treating schizophrenia patients [47].

The side-effect databases and digital application promote care delivery that is compliant with international regulatory advice for the treatment of depression and schizophrenia by promoting evidence-based, collaborative, and personalised prescribing decisions [48].

The authors therefore recommend that clinicians understand the anticholinergic burden of medications and the cumulative anticholinergic effects of several medications. They need to keep an eye out for anticholinergic syndrome symptoms in patients, recognise elderly or fragile patients or those with intricate co-morbidities who are using anticholinergic medications, and when feasible, minimise their use.

It is important to recognise and limit the use of medications that may negatively impact cognition, and if it is clinically acceptable, think about changing or quitting your prescription.

Declarations

Transparency declaration: We confirm that the manuscript is an honest, accurate, and transparent account of the literature being reported.

Author contribution statement: Both authors contributed to the literature search and to the writing up of the article and its review.

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