ARIPIPRAZOLE IN THE TREATMENT OF PSYCHOTIC BIPOLAR DISORDER

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Patients can have bipolar and psychotic symptoms at the same time. Aripiprazole has showed effectiveness in both areas in stabilising mood and reducing psychotic symptoms. Many patients, however, continue to suffer in their everyday life at the workplace, in relationships, and socially from fluctuating impairments. While the support of medication can be very effective and necessary, psychotherapy can focus on interactions with others and internal communication, that complement the successes of medication and go beyond them.

Keywords: psychosis, bipolar affective disorder, aripiprazole, antipsychotic, treatment, Communication-Focused Therapy®, CFT, psychotherapy, psychiatry

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Introduction

Psychosis is common in bipolar disorder. (Keck, McElroy, et al., 2003) Bipolar disorder is characterized by exacerbations of opposite mood polarity, ranging from manic to major depressive episodes. In the Diagnostic and Statistical Manual – 5th edition (DSM-5), it is conceptualized as a spectrum disorder consisting of bipolar disorder type I, bipolar disorder type II, cyclothymic disorder, and bipolar disorder not otherwise specified.

Schizoaffective disorder, which meets the criteria for a mood disorder and schizophrenia, can be found in the literature quite early in the 20th century. For example, an article in the American Journal of Psychiatry in 1933 describes a "group of 9 cases is presented in which there is a blending of schizophrenic and affective symptoms" (Kasanin, 1933) The article goes on to note that "[t]he psychosis is characterized by a very sudden onset in a setting of marked emotional turmoil with a distortion of the outside world and presence of false sensory impressions in some cases. The psychosis lasts a few weeks to a few months and is followed by a recovery." Interestingly they also observe that "[a] good social and industrial adjustment, the presence of a definite and specific environmental stress, the interest in life and its opportunities, and the absence of any passivity or withdrawal are some of the factors favoring recovery."

Psychotic bipolar disorder seems to be associated with differential impairment on tasks requiring frontal/executive processing, suggesting that psychotic symptoms may have neural correlates that are at least partially independent of those associated with bipolar I disorder more generally. However, deficits in attention, psychomotor speed, and memory appear to be part of the broader disease phenotype in patients with bipolar disorder. (Glahn et al., 2007) Aripiprazole, an atypical antipsychotic, first marketed in the early 2000s, has an effectiveness comparable to that of other first-line antipsychotic medications (Montastruc et al., 2019), but its pharmacodynamic properties and adverse effects profile differ.

Aripiprazole has been favoured because of its reduced metabolic adverse effects, compared with some other antipsychotic drugs.

Bipolar Disorder

Bipolar disorders (BPD) are major, life-long psychiatric illnesses found in 2–5% of the population. Syndromal recovery from acute episodes of mania or bipolar major depression is achieved in as many as 90% of patients given modern treatments, but full symptomatic recovery is achieved slowly, and residual symptoms of fluctuating severity and functional impact are the rule. (Huxley & Baldessarini, 2007) Depressive–dysthymic–dysphoric morbidity continues in more than 30% of weeks in follow-up from initial episodes as well as later in the illness-course. As few as one third of BPD patients achieve full social and occupational functional recovery to their own premorbid levels. (Huxley & Baldessarini, 2007) Treatment of all phases of this disorder is primarily with mood stabilizers, but many patients either show resistance to the conventional mood stabilizing medications or are intolerant to their side-effects. In this setting, second-generation antipsychotics have gained prominence as many bipolar subjects who are otherwise treatment refractory show response to these agents. (Muneer, 2016) Mood disorder-related psychotic symptoms in children and adolescents frequently reflect severe patterns of illness and require comprehensive assessment and sustained, multimodal treatment approaches. (McCarthy & Dobroshi, 2014)

Diagnosis

The diagnosis may sometimes not be so straight forward, particularly in cases with diffuse and complex mixed symptoms. Clinicians use heuristics when making diagnostic decisions instead of strictly adhering to diagnostic criteria. Meyer and Meyer investigated if the use of heuristics can explain when a diagnosis of psychotic disorder is given instead of bipolar disorder. The four versions of the case vignette all described the same person in a manic state and differed only in two aspects: the presence or absence of auditory hallucinations and of decreased need for sleep. The psychiatrists were asked to make a diagnosis, to rate their confidence in their diagnosis, and to recommend treatments. Almost half of the 142

psychiatrists (45%) did not diagnose bipolar disorder. Mentioning hallucinations decreased the likelihood of diagnosing bipolar disorder. The information about decreased need for sleep only affected the diagnosis significantly, if schizoaffective disorder was considered a bipolar disorder. Clinicians use heuristics when making diagnostic decisions instead of strictly adhering to diagnostic criteria. (Meyer & Meyer, 2009)

Neurobiology

More extensive prefrontal, thalamic, and hippocampal deficits might set apart schizophrenia and bipolar disorder. Initial comparative studies have suggested that patients with schizophrenia might show volume loss in middle prefrontal and thalamic regions (McIntosh et al., 2004), and in total hippocampal volume (McDonald et al., 2006). Another study suggested more widespread prefrontal and temporal grey matter loss in schizophrenia, but not inbipolar disorder, for which sparing of cortical changes was observed (McDonald et al., 2005). Results in a study by Nenadic and colleagues indicate that compared to healthy controls schizophrenia patients show grey matter deficits in medial and right dorsolateral prefrontal, as well as bilaterally in ventrolateral prefrontal and insular cortical areas, thalamus (bilaterally), left superior temporal cortex, and minor medial parietal and parietooccipital areas. Comparing schizophrenia vs. bipolar I patients yielded a similar pattern, however, there was an additional significant reduction in schizophrenia patients in the (posterior) hippocampus bilaterally, left dorsolateral prefrontal cortex, and left cerebellum. Compared to healthy controls, the deficits in bipolar I patients only reached significance for a minor parietal cluster, but not for prefrontal areas. (Nenadic et al., 2015) Future studies examining the neurobiology of treatment response in bipolar depression, as well as longer-term trials with various compounds, focusing on treatments acting on differing poles of illness are required. (Jauhar & Young, 2019)

Dopamine Hypothesis

The dopamine hypothesis predicts that dopamine hyperactivity in the mesolimbic pathways of the brain (also known as reward pathways) causes delusions, hallucinations and disorganized thoughts. Dopamine inactivity in the mesocortical pathways (involved in cognitive control, motivation and emotional response) and the prefrontal cortex (an area implicated in planning complex cognitive behaviour and moderating social behaviour) leads to an impairment in linguistic ability, an inability to experience pleasure, and autism. Aripiprazole's effects at dopamine receptors are thought to decrease dopamine production in some areas (and possibly raise them in others) and stabilize the dopamine system.

Dopamine synthesis capacity seems elevated in bipolar psychosis and is associated with positive psychotic symptoms, irrespective of diagnosis. In a cross-sectional case-control positron emission tomographic study of 22 individuals with first-episode bipolar psychosis, 16 individuals with first-episode schizophrenia, and 22 controls, there was a statistically significant elevation in dopamine synthesis capacity in those with bipolar psychosis compared with controls. This difference was similar to that seen in schizophrenia, and there was a statistically significant association between positive psychotic symptoms and dopamine synthesis capacity in the whole sample, explaining 27% of the variance. (Jauhar et al., 2017)

Aripiprazole

Aripiprazole (e.g., Abilify®) is an atypical antipsychotic used mainly to treat schizophrenia and bipolar disorder. It is also used for psychotic and mood disorders in youth, and it is being investigated for a potential role in the treatment of cocaine addiction. It has been applied as an add-on treatment for major depressive disorder, tic disorders, obsessive-compulsive disorders (OCD), and irritability associated with autism. Clinical experience with aripiprazole appears to have confirmed the effectiveness and the safety in patients with schizophrenia as well as for the treatment of mania in type I bipolar disorder. (Di Sciascio & Riva, 2015) Aripiprazole, effective against positive and negative symptoms, is a safe and well-tolerated potential treatment for schizophrenia and schizoaffective disorder. (John M. Kane, 2002) The drug was first

approved by the US Food and Drug Administration (FDA) for use in schizophrenia in 2002. Aripiprazole can be effective in treating the acute manic episodes of bipolar disorder in adults, adolescents and children. However, its effect is only useful for the manic phases with little or no effect on the depressive phases. For this reason, aripiprazole is often used in conjunction with mood stabilizers. This dual approach is effective, but it increases the risk of movement disorders (extrapyramidal symptoms).

Aripiprazole exhibits the pharmacodynamic properties of partial agonism, functional selectivity, and serotonin-dopamine activity modulation. (Muneer, 2016) Aripiprazole exerts its impact via various receptors including multiple subtypes of serotonin, dopamine, adrenergic, muscarinic acetylcholine and histamine receptors. It also works on serotonin, norepinephrine and dopamine transporter proteins.

Bipolar Disorder

Second generation antipsychotics are increasingly used for maintenance treatment in bipolar disorder, as monotherapy or adjunctive therapy. Although lumped together as one class, their pharmacological properties, efficacy and tolerability in bipolar disorder are varied. (Jauhar & Young, 2019) Randomized controlled trials with aripiprazole have been conducted in various phases of bipolar disorders. (Muneer, 2016) Aripiprazole has been found to be efficacious in the treatment and prophylaxis of manic and mixed episodes but has not shown effectiveness in acute and recurrent bipolar depression. (Muneer, 2016)

In a 2003 multicentre, double-blind study with 262 randomly assigned bipolar disorder patients in an acute manic or mixed episode, aripiprazole showed significantly greater efficacy than placebo for the treatment of bipolar disorder patients in acute manic or mixed episodes and appeared safe and well tolerated. (Keck, Marcus, et al., 2003). In another 2008 double-blind study with acutely manic bipolar patients and 516 participants, aripiprazole significantly reduced total scores on the Young Manic Rating Scale compared with placebo in patients with more severe or less severe illness, with mixed or manic episodes, with or without psychotic features, or with a history of rapid or non-rapid cycling. (Suppes et al., 2008) A meta-analysis of four randomised controlled trials on acute mania suggested that the effect size of aripiprazole versus placebo was equal to 0.14 but a more reliable and accurate estimation is 0.18 for the total Positive

and Negative Syndrome Scale (PANSS) score. The effect was higher for the PANSS-positive subscale, PANSS-hostility subscale and PANSS-cognitive subscale, and lower for the PANSS-negative subscale. (Fountoulakis et al., 2009) In another meta-analysis, aripiprazole improved acute mania and psychosis in the acute mania state but did not improve depressive symptoms in the acute depressive state. Aripiprazole was also associated with lower relapse rates in bipolar mania when used in combination versus a placebo in maintenance therapy and lower dropout rates (Li et al., 2017). Extrapyramidal side effects in the maintenance phase did not show a higher rate than in placebo or lithium.

Long-Acting Formulations

For people who are intolerant or unable to adhere to lithium use, maintenance treatment with antipsychotics seems reasonable, with individualized care regarding side effects and their management- and possible use of other agents for prevention of depression, in conjunction with adequate monitoring monitoring (Bauer et al. 2018). A long-acting injectable formulation of aripiprazole (AOM 400) is also used in bipolar disorder. In one study, patients were stabilized on oral aripiprazole, cross-titrated to AOM 400, then randomized in a 52-week, double-blind, placebo-controlled, withdrawal phase. AOM 400 significantly increased time to hospitalization for any mood episode versus placebo, and Young Manic Rating Scale total scores, which had decreased with oral aripiprazole, could be maintained with AOM 400. (Calabrese et al., 2018)

Psychosis

Schizophrenia and bipolar disorder overlap considerably. Schizophrenia is a primary psychotic disorder, whereas approximately half of people with bipolar disorder will experience psychosis. (Bowie et al., 2018) There is accumulating evidence that these two disorders overlap in neuroimaging, neuropsychological, histological, and clinical features. Several studies have shown shared genetic aetiology between bipolar disorder and schizophrenia. A study with a cohort of 927 bipolar patients showed that bipolar disorder type I with manic psychosis was genetically more similar to schizophrenia than any other tested bipolar subgroup. (Markota et al., 2018)

There is a wide range of antipsychotics that can be used in bipolar patients with psychosis. Primarily the atypical (or second generation) antipsychotics in clinical because of their better assumed side effect profile. In a prospective, randomized, open-label study between October 2005 and January 2011 with two hundred-two first-episode, drug-naïve patients with first episode psychosis discontinuation rates were lowest for aripiprazole relative to ziprasidone and quetiapine. No significant differences were found in the profile of extrapyramidal symptoms, however. (Gómez-Revuelta et al., 2018) Patients on aripiprazole were more likely to be prescribed benzodiazepines, which could be explained by the fact that aripiprazole has in clinical experience a lower sedating effect and is usually less effective against anxiety.

Long-Acting Formulations

A 2018 literature review, which included 28 papers with randomised assignment of aripiprazole LAI formulations in schizophrenia and bipolar disorder, found that aripiprazole LAI may be efficacious in reducing relapse of schizophrenia and bipolar disorder in the long term in stabilised patients and in improving symptoms of schizophrenia during its acute phase, with both monohydrate and lauroxil formulations showing efficacy. (Rapinesi et al., 2019) A study with 143 patients with a diagnosis of schizophrenia or schizoaffective disorder suggested early administration and longer duration of aripiprazole or paliperidone treatments could play a significant role in improving global functioning of patients with schizophrenia and schizoaffective disorder. Better improvement in functioning could be achieved with aripiprazole in young individuals with recent illness onset and paliperidone in patients at risk for recurrent hospitalisations. (Girardi et al., 2018)

Schizoaffective Disorder

In a literature review of clinical studies of atypical antipsychotics and meta-analyses of trials comparing first- and second-generation antipsychotics in the treatment of schizophrenia or schizoaffective disorder between 1999 and May 2009, aripiprazole monotherapy appeared to be effective and well tolerated in treating the positive, negative, and cognitive symptoms of schizophrenia and schizoaffective disorder. It was associated with a low risk for the common adverse effects of antipsychotic therapy, including

metabolic and endocrine alterations. (Stip & Tourjman, 2010) In a prospective, multicentre, single-group, 26-week open multi-centre study of 300 patients with schizophrenia, schizophreniform disorder, and schizoaffective disorder, aripiprazole demonstrated effectiveness in the long-term treatment of both positive and negative symptoms of psychosis. (Kwon et al., 2009)

Young People

In a 2012 literature review, treatment with aripiprazole was associated with significant reduction of the Positive and Negative Symptom Scale (PANSS) scores in youth with schizophrenia, and reductions in items in the negative symptom scores at higher doses (30 mg/day). Significant reductions in the Young Mania Rating Scale (YMRS) have been demonstrated in youth with bipolar disorder. In mixed populations, reductions in the Clinical Global Impressions Scale (CGI-S) have also been demonstrated when compared with treatment with placebo. Treatment with aripiprazole was reported to have a lower incidence of weight gain, and less elevation of prolactin. At higher doses, it appeared more likely to result in extrapyramidal symptoms and tremor. (Doey, 2012)

Augmentation

In a small study with seven patients, the augmentation of clozapine with aripiprazole appeared safe and effective in severe psychotic schizoaffective and bipolar disorders which failed to respond to atypical antipsychotics. A possible pharmacokinetic interaction between clozapine and aripiprazole does not account for the improved clinical benefit obtained after aripiprazole augmentation. (Benedetti et al., 2010) In a multicenter, randomized, placebo-controlled study including outpatients experiencing a manic or mixed episode (with or without psychotic features), adjunctive aripiprazole therapy showed significant improvements in mania symptoms as early as the first week and demonstrated a tolerability profile similar to that of monotherapy studies. (Vieta et al., 2008)

Problems

Some of the problems associated with aripiprazole are shared with other antipsychotics, while some are distinct. Aripiprazole, like other dopamine modulating antipsychotics, can induce neuroleptic malignant syndrome, a potentially life-threatening neurological disorder consisting of muscle rigidity, fever, delirium or coma and autonomic instability. Research has found an increased risk of death with use of aripiprazole in older patients with dementia-related psychosis, due to cerebrovascular events, or adverse effects on the circulatory system in the brain. There have also been some reports of psychotic symptoms getting worse when switching from another antipsychotic, and in the clinical trials there was, among other issues, a possibility of worsening suicidal thoughts in children and adolescents. The following gives three examples of adverse effects and some (incomplete) notes on them from the literature.

Metabolic Syndrome

Metabolic syndrome and its components are highly predictive of cardiovascular diseases. People treated with all individual antipsychotic medications seem to have a significantly higher risk of metabolic syndrome compared to antipsychotic-naïve participants. In a literature review study, the risk was significantly higher with clozapine and olanzapine (except vs. clozapine) than other antipsychotics, and significantly lower with aripiprazole than other antipsychotics (except vs. amisulpride). Compared with matched general population controls, people with severe mental illness had a significantly increased risk for metabolic syndrome and all its components, except for hypertension. (Vancampfort et al., 2015)

Worsening of Psychotic Symptoms

In a systematic literature review in 2012, there were indications that in some patients, psychotic symptoms may worsen after adding aripiprazole to the current regimen (in eight cases). Besides psychotic symptoms, increasing agitation (nine cases), aggression (11 cases), and/or activation (seven cases) were reported. Clinical resolution occurred after aripiprazole discontinuation in eight cases. (Takeuchi & Remington, 2013) However, in a 2018 meta-analysis by the same study leader, utilizing a total of 22 studies (13 switching and 9 adding

studies) involving 5,769 patients, findings suggested that there was no direct evidence that a switch to aripiprazole was related to risk of psychotic worsening in participants in clinical trials, although a switch to aripiprazole may have been associated with a higher risk of study discontinuation due to lack of efficacy. (Takeuchi et al., 2018)

Gambling

In one report, three cases of pathological gambling were likely induced by aripiprazole in patients with schizophrenia or schizoaffective disorder. All three patients had no history of pathological gambling, and they started gambling after initiation of treatment with Aripiprazole. The fact that pathological behavior disappeared quickly when the medication ended suggests that an elaborate behavioral manifestation could be related to dopaminergic tone in patients with schizophrenia. (Cohen et al., 2011) Another report described six cases with first-episode psychosis in whom problematic gambling emerged while on aripiprazole and urged caution with aripiprazole in patient populations where problematic gambling could be a potential issue. (Corbeil et al., 2020)

Psychotherapy

Pharmacotherapy, though the accepted first-line treatment for patients with bipolar psychotic disorder, is insufficient by itself, encouraging development of adjunctive psychological treatments and rehabilitative efforts to further limit morbidity and disability. Psychotherapy can be helpful in both cases, psychosis and bipolar disorder. Jung and Newton identified a total of 28 interventions from a systematic search and review of the Cochrane Reviews for either schizophrenia, psychosis, schizoaffective, or bipolar disorder. Of the 28 interventions identified in this review, four had strong support and five had moderate support meriting application. (Jung & Newton, 2009)

Several psychotherapeutic approaches have shown at least some effectiveness in the treatment of psychotic and bipolar symptoms. Interpersonal, cognitive–behavioural, and psychoeducational therapies all show promise for improving symptomatic and functional outcomes. Much less is known about how

these and more specific rehabilitative interventions might improve vocational functioning. (Huxley & Baldessarini, 2007) Mentalization-based psychodynamic psychotherapy for disturbances of awareness of the self and others in patients with psychotic-spectrum disorders has been used with some success. (B. Brent, 2009) In a study of the Danish schizophrenia project (DNS), which compared supportive psychodynamic psychotherapy for psychosis with standard treatment in patients with a first-episode schizophrenia spectrum disorder, the intervention group improved significantly on measures of both PANSS and GAF scores, with large effect sizes at two years follow-up after inclusion. Combination with treatment as usual also seemed better than treatment as usual lone. (Rosenbaum et al., 2012)

Psychotic and bipolar symptoms both have an effect on depression. In general, subclinical psychotic experiences have a negative impact on the course and outcome of psychotherapy in MDD, while effects of subclinical bipolar experiences seem less prominent. In a naturalistic study, patients with MDD (n=116) received psychological treatment (cognitive behavioural therapy or interpersonal psychotherapy) alone or in combination with pharmacotherapy. Depression and functioning were assessed six times over two years. Lifetime psychotic experiences and bipolar symptoms were assessed at the second time point. Subclinical psychotic experiences predicted more depression over time, non-remission and relapse. Subthreshold bipolar symptoms predicted relapse (Wigman et al., 2014)

Third-wave psychological interventions have gained relevance in mental health service provision but their application to people with psychosis is in its infancy and interventions targeting wellbeing in psychosis are scarce. Schrank and colleagues provided initial support for the feasibility of a course of positive psychotherapy adapted in people with psychosis, positively affecting symptoms and depression. (Schrank et al., 2016)

It also needs to be added that some populations may have been overlooked in treatment research, even though identifying effective therapies would be very important. For example, the perinatal period is associated with an increased risk of severe mental disorders. Despite the importance of perinatal episodes, with suicide a leading cause of maternal death, few studies are available to guide the management of women with severe mental disorders in pregnancy and the post-partum period. (Jones et al., 2014)

Insight

Poor insight impedes treatment in early phase psychosis. Different psychotherapeutic approaches differ in their focus on insight. At one end of the spectrum, a novel metacognitively oriented integrative psychotherapy, Metacognitive Reflection and Insight Therapy, for individuals with early phase psychosis, for example, has shown success in improving insight in a small study sample. (Vohs et al., 2018) Psychodynamic psychotherapy as one of the large established therapies also has a central focus on insight.

Narrative

There is ongoing debate about both the value of psychotherapy in psychotic disorders and the best type of psychotherapy to use if necessary. A narrative psychotherapy approach using dialogical theory and therapy ideas is a reasonable approach for the psychotherapy of psychosis. Review of psychotherapy notes showed that narrative approaches allowed the therapist to align with the patient as collaborator in considering the story presented and was therefore less productive of defensiveness and self-criticism than conventional approaches. The therapy included techniques for negotiating changes in illness narratives, identity narratives, and treatment narratives that were more conducive of well-being and recovery. (Mehl-Madrona & Mainguy, 2017)

Mentalization

Mentalization is the ability to understand the mental state of oneself or others that underlies overt behaviour. It is a product of communication, internal and external, and it helps in communicating with others. Mentalization helps us to understand others and the world around us. It also facilitates our own understanding about ourselves, since external and internal communication reflect each other (Haverkampf, 2010, 2018). It goes beyond thinking about thinking, because the information that plays a

role in mental processes that can manifest in behaviours does not include only thoughts. Disturbances of mentalization have been increasingly associated with the symptoms and functional impairment of people with psychotic disorders. It has been proposed that psychotherapy designed to foster self and other understanding, such as mentalization-based treatment, may play an important part in facilitating recovery from psychosis. (B. K. Brent et al., 2014) In a review of 17 articles, benefits of the CCBT approach (Mindfulness and Acceptance-based interventions, Compassion-Focused Therapy, Dialectical Behavior Therapy, and Metacognitive Therapy) for the psychosis continuum regarding clinical variables such as psychotic symptoms, anxiety and depression, functioning or quality of life were found. (Martins et al., 2017)

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