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# Optimizing Clozapine Treatment

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**Key words:** Clozapine, pharmacotherapy, effect, side effect

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This lecture will focus on the clinical use of clozapine. It remains underutilized because of realistic concerns about its side effects, because of the extra time it takes to initiate and manage a patient on clozapine, but also because some clinicians lack experience with it: this lecture will be particularly supportive to them. First, there will be a review of appropriate evidence-based indications for clozapine, and an examination of the place of clozapine in the sequence of trials recommended in different psychopharmacology algorithms for schizophrenia that have been developed. All algorithms suggest use of clozapine after unsatisfactory response to two or at the most three adequate monotherapy trials of antipsychotic drugs. Before clozapine, patients should have the opportunity to try one or more of the possibly more effective antipsychotics: olanzapine, risperidone, and first-generation neuroleptics such as perphenazine. Olanzapine is not first line due to its metabolic toxicity. Clozapine can be particularly effective for people with suicidal behavior (treatment-resistance not required in this case), assaultive behavior, substance abuse, polydipsia/hyponatremia, and nonadherence histories.

The pre-treatment workup will be presented followed by a discussion of issues in the informed consent process for clozapine with both competent and incompetent patients. Getting consent to clozapine is facilitated by having the ability to present an appropriately positive and convincing description of the potential benefits of this medication and its ability to improve quality of life.

Next, dosing strategies will be reviewed for different age groups, including the role of plasma levels; optimal results occur at levels over 350-450 ng/ml of the parent compound. Contingencies such as dose interruptions and drug interactions will be discussed. For example, heavy cigarette smokers can have very low clozapine levels, and patients on fluvoxamine will get extremely high levels if the dose is not lowered.

Side effects will then be discussed. Neutropenia is sometimes benign (as in the cases of benign ethnic neutropenia and morning pseudoneutropenia) and might not require discontinuation of clozapine and may be managed successfully. Agranulocytosis must not be rechallenged, however, and treatment with granulocyte colony stimulating factor may be necessary. Seizures are a common problem but usually do not require stopping clozapine. Valproate is perhaps the best anticonvulsant to employ. Myocarditis and cardiomyopathy are life-threatening complications that need to be detected early: be suspicious if the patient develops tachycardia accompanied by fever, fatigue, dyspnea, chest pain, and flu-like symptoms. Weight gain, metabolic syndrome, and insulin resistance are well-known problems that often pose difficulties. A few medication treatments for this have had modest success (metformin, topiramate) but proper nutrition and exercise are the mainstays which patients may be more willing to pursue when they improve clinically. Constipation is a major side effect in up to 15% of patients, can be life-threatening, but often can be avoided with a high fiber diet, adequate hydration, exercise, and stool softeners. Other clozapine side effects are relatively minor but can be very annoying for patients and become a threat to their compliance: sedation (caffeine may help), hypersalivation

(many possible remedies, few proven), tachycardia (beta-blocker may be necessary), hypotension/dizziness (hydration, support-hose), and obsessive-compulsive symptoms (sertraline may be the preferred medication treatment) are in this category. Rebound psychosis after abrupt discontinuation of clozapine can be severe but it may help to use an anticholinergic to minimize cholinergic hypersensitivity associated with clozapine withdrawal.

# Use and Misuse of Antipsychotics (Typical and Atypical) in Resistant Anxiety

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Although selective serotonin reuptake inhibitors (SSRIs) have revealed new avenues for OCD treatment, about 40% of patients do not respond, or respond only partially to this approach. In those resistant patients, the possibility of adding on antipsychotic, and especially the new atypical antipsychotic is often raised.

Data in regard to augmentation of OCD patients who did not respond to treatment with SSRI suggest that risperidone might have a specific therapeutic potential in this subset of patients. The role of antipsychotics with 5HT1D properties like ziprasidone need to be studied.

The data supporting the role of antipsychotic medication in obsessive compulsive disorder with poor insight are not convincing. However, at times the treatment dilemma (antipsychotic or antiobsessive) actually derives from diagnostic ambiguity; many of the very severe ego-syntonic obsessive compulsive patients may be erroneously diagnosed as schizophrenic, while they are actually severe OCD, and as such should be treated initially with antiobsessive medication and not antipsychotic. In fact, there is data to suggest that poor insight is not related to treatment outcome with SSRI in OCD, so there is no reason to suggest that an antipsychotic is always of extra benefit in these cases.

The prevalence of OCD amongst schizophrenic patients ranges from 10-25% and has a negative effect on the prognosis for that substantial proportion of schizophrenic patients. In the past, a diagnosis of comorbid schizophrenia and OCD was not possible, but the DSM IV introduced it as a viable comorbidity. It is specified, however, that the obsessions must not be restricted to the delusional content of the schizophrenia presentation. Preliminary data implies that for this subset of patients (the schizo-obsessive patients) a combination of antipsychotic and antiobsessive medication might be useful.

In OCD with tic disorder, combination treatment using highly potent dopamine blockers and selective serotonin inhibitors is effective. However, the use of dopamine blockers in OCD is not limited to this subset of patients; dopamine blockers such as risperidone and quetiapine are effective augmentation therapy in treatment-resistant patients. Some of the most severe cases are those in which the family is involved in "helping" the patient. Unless patients undergo detailed and well-planned cognitive-behavioral therapy, along with careful evaluation and assessment of the family environment, they cannot be considered "resistant." For those patients who are actually resistant, neurosurgery, gamma knife treatment and, more recently, deep brain stimulation have been proposed, but

these should be reserved as last-resort options.

With advances in our understanding of the complexity of OCD and OCRDs, it may be possible to tailor treatment to the specific needs of individual patients. Sophisticated pharmacologic interventions and treatment that takes environmental factors into account, along with improvements in diagnostic skills, all provide new hope for this intriguing group of patients with OCD.

There is also some data about use of antipsychotics in PTSD, in generalized anxiety disorder, social phobia and other anxiety disorders. However, there is still much research to be done about the benefits of different antipsychotic medications, either as augmentation to current medication or as monotherapy, in anxiety disorders.

# Pharmacotherapy in Children and Adolescents with Bipolar and Co-occurring Psychiatric Disorders

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**Key words:** Pharmacotherapy, children and adolescents, bipolar disorders, co-occurring psychiatric disorders

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To examine the tolerability, safety and efficacy of pharmacological treatments for children and adolescents with bipolar and other co-occurring psychiatric disorders.

We will review findings from recent studies of pharmacological treatments for children and adolescents with bipolar disorder as well as examine treatment strategies for bipolar youth with co-occurring psychiatric disorders.

The results from recently completed double-blind placebo controlled studies of treatments for bipolar youth will be presented. In general, results of these studies indicate that atypical antipsychotics may be more effective than classic mood stabilizers for manic adolescents, however, the long-term safety of these agents has not yet been explored. Furthermore, recent studies reveal the effectiveness of pharmacological agents for the treatment of bipolar youth with depression. However, there are few studies examining the effects of combination pharmacological interventions for the treatment of co-occurring disorders associated with pediatric bipolar disorder. Studies suggest that specific atypical antipsychotics have distinct risks for metabolic side effects.

Data supporting the use of pharmacological agents for the treatment of bipolar disorder in children and adolescents are rapidly expanding. However, there are few studies examining pharmacological treatment options for the prevention of recurrent mood episodes. Additionally, studies examining the long-term safety and tolerability of pharmacological agents for bipolar youth as needed.

# Does the Glutamatergic System Play a Pathophysiological Role in Mood Disorders? Results from a Clinical Approach Testing This Hypothesis

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**Key words:** Glutamatergic system, mood disorders, neuroplasticity

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Structural neuroimaging studies in patients with mood disorders have demonstrated regional volumetric reductions in various grey matter areas. These changes have also been observed in post-mortem neuropathological studies, in which region- and layer-specific reductions in number, density, and/or size of neurons and glial cells have been reported. It is becoming evident that these abnormalities may be associated with phenomena of cellular plasticity. These are described as the capacity of neuronal and glial cells to resist or adapt to environmental stressors (cellular resilience), which may translate into the ability to undergo re-modeling of synaptic connections (synaptic plasticity) and/or cell regeneration (neurogenesis). Increasing evidence suggests that abnormal activity of the glutamatergic system of neurotransmission, partly regulated via glucocorticoids and stress mechanisms, might be involved in the pathogenesis of impairments in cellular neuroplasticity observed in subjects with mood disorders.

The glutamatergic neurotransmission involves a complex system of receptors that includes ionotropic (namely NMDA, AMPA, or Kainate receptors) and metabotropic receptors. Importantly, dysfunctional glutamatergic neurotransmission can result in activation/deactivation of intracellular cascades associated with trophic support, and neuronal or glial death. These changes may be partially mediated by an increased NMDA receptor throughput, predisposing the cell to neurotoxicity-related events. Thus, it is proposed that decreases in glutamate neurotransmission in such systems may result in enhancement and maintenance of neural connectivity mechanisms, which are essential for healthy affective functioning.

It remains unclear what aspects of glutamatergic modulation (i.e., direct inhibition of the release of glutamate, direct effects at the ionotropic and/or metabotropic receptors) are necessary to mediate the antidepressant effects. Therefore a series of clinical studies of candidate glutamatergic drugs available for human utilization were investigated in the treatment of mood disorders at the Mood and Anxiety Disorders Unit, National Institute of Mental Health (Bethesda MD, US). Riluzole, an inhibitor of glutamate release, was tested in an open-label study with 19 treatment-resistant depressed patients (53% of them were classified as having stage 2 treatment resistance or greater) who received riluzole monotherapy at a mean dose of 169 mg/day for 6 weeks. In a separate study, subjects with bipolar depression were administered Riluzole in combination with lithium and treated for 8 weeks. A study designed to assess possible antidepressant effects of memantine, a selective non-competitive NMDA receptor antagonist, was conducted in a double-blind, placebo-controlled study in subjects with major depression: 32 subjects were randomly assigned to receive memantine (5–20 mg/day) or placebo for 8 weeks. Ketamine, an NMDA receptor antagonist primarily used for the induction and maintenance of general anesthesia, was investigated in a randomized, double blind, placebo-controlled, crossover study, and the speed of onset was also assessed. Eighteen subjects with treatment-resistant

major depression received an intravenous infusion of either ketamine hydrochloride (0.5 mg/kg) or placebo on 2 test days, one week between dosing.

The results of these studies will be presented for discussion. These studies validate the need to better understand the role of the glutamatergic neurotransmission in the pathophysiology of mood disorders. This neurotransmitter system and the associated intracellular signaling cascades may represent a viable target for the development of new antidepressant interventions for the treatment of these devastating illnesses.

# Electrical Stimulation of The Dorsolateral Periaqueductal Gray Evokes Escape Response Followed by Fear Behaviour in Rats

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**Key words:** Electrical stimulation, fear behaviour, dorsolateral periaqueductal gray

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Electrical stimulation of the dorsolateral periaqueductal gray (dlPAG) has been shown to induce escape and freezing responses which mimic the panic- and fear-like behaviour. In the present study, we tested the hypothesis whether the freezing behaviour could be attenuated by acute and chronic administration of escitalopram and buspirone. Additionally, the levels of blood corticosterone were measured in the different experimental conditions. Our results demonstrated that escitalopram treatment was effective in attenuating the stimulation induced fear when compared to buspirone and saline treated animals after acute and chronic treatment. The stimulation amplitudes to evoke escape behaviour were significantly higher after chronic buspirone and escitalopram treatment. The levels of blood corticosterone were increased after stimulation and the open-field testing conditions when compared to the baseline level. In conclusion, the current study shows that the escape reaction generated intrinsically within the dlPAG was followed by freezing behaviour 12 h later. This fear-like behaviour was reversed by escitalopram treatment while buspirone or vehicle treated groups did not attenuate fear behaviour. Our data also confirm the elevation of blood corticosterone level during the panic and fear-like behaviour. Future research of fear should be focused on the underlying neural mechanism within the dlPAG.