Addition of amoxapine improves positive and negative symptoms in a patient with schizophrenia

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Introduction

Amoxapine is a tricyclic antidepressant of the dibenzoxazepine class with a heterogeneous receptor binding profile, mainly monoamine reuptake inhibition plus antagonism of 5-HT 2a and D4/D2 receptors [Kapur *et al.* 1999]. It is an inhibitor of both norepinephrine (NE) and serotonin (5-HT) reuptake with K_d values of 16 and 58 nM, respectively [Tatsumi *et al.* 1997]. It also blocks 5-HT and dopamine (DA) receptors: at a dose of 150 mg/day amoxapine displayed 98% 5-HT₂ occupancy and 63% D2 receptor occupancy by brain positron emission tomography (PET) in normal volunteers [Kapur *et al.* 1999]. In addition to its effects on monoamines, amoxapine acts on other neurotransmitter systems. It is a potent inhibitor of glycine transporters GLYT1b and GLYT2a [Núñez *et al.* 2000], and it activates delta-opioid receptors in human frontal cortex *in vitro* [Onali *et al.* 2010]. In addition, amoxapine has been shown to inhibit several K⁺ channels including the voltage-gated K⁺ [He *et al.* 2010] and the G protein-activated inwardly rectifying K⁺ (GIRK) channels [Kobayashi *et al.* 2011] at micromolar concentrations, the same range as the brain concentration of the drug during treatment (5–67 μ M); this effect seems to be mediated through serotonin and dopamine D1/D5 receptors [Yang *et al.* 2011].

Amoxapine is metabolized *in vivo* via CYP2D6 to 7-hydroxyamoxapine, which has affinity for 5-HT_{2a} and D2 receptors. It is also metabolized to 8-hydroxyamoxapine via CYP1A2 [Wong *et al.* 2012]. These various sites of action on neurotransmitters and ion channels give amoxapine a unique pharmacological profile that may be relevant for its therapeutic activity and side effects. Tardive dyskinesia and neuroleptic malignant syndrome have been described with amoxapine

and attributed to its blockade of DA receptors, while seizures may be related to its activity on ion channels.

Amoxapine has demonstrated efficacy in major depressive disorder, with and without psychotic features [Gelenberg *et al.* 1984; Anton and Burch, 1990]. Its use in schizophrenia is not as well documented. Although one small randomized placebo-controlled study of 10 schizophrenia patients did not find improvement after amoxapine [Fitzgerald *et al.* 2004], an open-label [Apiquian *et al.* 2003] and two double-blind trials demonstrated efficacy similar to risperidone and haloperidol in the treatment of psychosis, with additional improvement in negative symptoms [Chaudhry *et al.* 2007; Apiquian *et al.* 2005].

Here, we report the improvement, following amoxapine initiation, of positive and negative symptoms in a patient with schizophrenia who had shown lack of clinical response to a robust antipsychotic regimen. This case highlights the use of amoxapine for augmentation with potential to improve positive and negative symptoms of schizophrenia.

Case presentation

The patient is a 26-year-old White female, diagnosed with schizophrenia, paranoid type, since a psychotic episode as a sophomore in college. She presented to our emergency room with local police and was hospitalized, as she was unable to care for herself. She displayed disorganized thoughts with bizarre and persecutory delusions. The patient had four previous admissions: 2004 for psychosis, 2005 for a suicide attempt by overdose, and 2006 and 2010 for psychosis. Admission medications at the time of the first hospitalization

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were olanzapine, quetiapine, bupropion and escitalopram. Psychotic symptoms improved with haloperidol, followed by haloperidol decanoate and oral risperidone. Bupropion was continued. Divalproex was trialed due to concern for possible bipolarity, but discontinued due to lack of efficacy. Bipolar disorder was not diagnosed. All medications were discontinued during the second hospitalization due to a 'lack of stated psychotic or mood symptoms'. Her third admission was notable for a trial of lorazepam due to concern for catatonia, based on isolation, social withdrawal and slowed responses. No improvement was noted and catatonia was ruled out. Trials of sertraline and lithium to target flat affect 'due to schizophrenia' and social withdrawal were also ineffective. She was discharged on risperidone extended release injection. Her fourth admission resulted in minor improvement of psychotic symptoms with the combination of haloperidol and risperidone. Bupropion was again trialed for amotivation and social withdrawal, but was ineffective. She was discharged to an institutional setting and started on clozapine, which was discontinued due to agranulocytosis. Cannabis, cocaine and alcohol use was reported only in 2004 and 2005, and all admission toxicology screens were negative. Family psychiatric history was notable for a maternal diagnosis of schizophrenia. Social history revealed residence with her mother, and the presence of a guardian. Mental status exam was notable for disheveled appearance, blunted affect, hostile behavior, disorganized thought process and persecutory delusions. Medical history and admission laboratory tests were unremarkable.

Based on previous response, risperidone was initiated, and increased to 8 mg daily. Haloperidol decanoate 100 mg was given after 9 days. No improvement in symptoms was noted after 6 weeks of hospitalization. The search for alternatives led to consideration of loxapine and, after literature review, its *N*-demethylated derivative and active metabolite, amoxapine. Amoxapine was initiated at 50 mg and titrated to 200 mg, consistent with effective dosing in previous studies [Chaudhry *et al.* 2007; Apiquian *et al.* 2005]. Risperidone was reduced concurrently to 6 mg daily. Before amoxapine, Positive and Negative Symptom Scale (PANSS) positive scale score was 31, negative scale 41 and general psychopathology scale 50. Composite Bush–Francis score was three, with points given for staring and mutism. These scores were considered to be equivalent to the patient's condition on admission. Within 7

days of amoxapine, the patient began to participate in social activities on the unit, and tolerated brief interviews. Range of affect broadened during the subsequent week, to the extent of smiling reactively. Discharge PANNS scores, 14 days after initiation of amoxapine, were 21, 39 and 38, respectively, and the patient returned a handshake with the team prior to exiting the unit.

Discussion

Amoxapine's inhibition of 5-HT and NE reuptake, D2/D4 and 5-HT_{2a} antagonism and GLYT1 inhibition (possibly leading to increased NMDA activity via increased glycine availability) [Field *et al.* 2011], represented a unique addition to the current antipsychotic regimen for this patient. Potentially, improvement could be attributed to delayed response to risperidone and haloperidol; however, dose reduction of risperidone, undertaken after initiation of amoxapine, did not lead to decompensation. Further, haloperidol decanoate serum concentration would have peaked in 7 days and its half-life is 21 days. No symptomatic improvement occurred near these dates. Further, the improvement in negative symptoms is inconsistent with effect of a typical antipsychotic. Catatonia could explain the patient's treatment resistance; however, she displayed relatively few features of this syndrome, and previous trials of benzodiazepines for identical symptoms were ineffective. Mood etiologies were considered, however, the patient did not display symptoms of depression, beyond the noted affect restriction. Thus, we believe adjunctive treatment with amoxapine was responsible for the patient's substantial improvement, and may be due to its specific pharmacological characteristics.

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Declaration of Conflicting Interest

The authors declare that there are no conflicts of interest.

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