When the drugs don’t work: treatment-resistant schizophrenia, serotonin and serendipity

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Abstract: Treatment-resistant schizophrenia is a serious clinical problem. We adopt a systems-level approach positing a greater role for cognitive control mechanisms in the development of psychotic symptoms and illustrate the clinical application of this via a case report of treatment-resistant patients treated successfully with adjunct pro-cognitive serotonergic medication.

Keywords: cognition, novel treatment, refractory schizophrenia

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Background

Treatment resistance in schizophrenia remains a difficult problem, with up to 40% of diagnosed patients showing inadequate response to optimal antipsychotic treatment. These patients fulfill criteria for treatment-resistant schizophrenia (TRS), based on at least two prior drug trials of 4–6 weeks’ duration with no clinical improvement, persistence of illness for longer than 5 years with no period of good social or occupational functioning, and persistent psychotic symptoms as defined as a score of at least 4 (moderate) on at least two positive symptom items of the Positive and Negative Syndrome Scale (PANSS). More recent data from first episode studies suggest that in the majority of patients with TRS, treatment resistance is evident at their first presentation. All current antipsychotic medication acts through modulating dopamine receptors, with treatment resistance occurring despite adequate D2 receptor occupancy by antipsychotic medication, suggesting that mechanisms other than hyperdopaminergia are driving psychotic symptoms in treatment resistance. Treatment-resistant patients show more robust cognitive deficits compared to treatment responders, and stronger cognitive performance is associated with a more favourable clinical outcome. While our knowledge of cognitive control mechanisms has grown in recent years, through the advent of functional neuroimaging, the key neurophysiological underpinnings of these deficits remain unclear.

At the systems level, schizophrenia can be viewed as a disconnection syndrome, with frontostriatal interactions specifically postulated to be crucial in symptom formation. In this view, NMDA receptor hypofunction results in decreased input from the prefrontal cortex to the midbrain, which in turn, through inhibition of GABA interneurons, results in overactivation of dopamine neurons projecting to the striatum. The resulting hyperdopaminergia is associated with a state of aberrant salience, whereby irrelevant environmental stimuli are imbued with special significance and the individual develops bizarre ideas or delusions in order to explain these experiences of salience. At the same time, a failure of top-down control signals from prefrontal areas to widespread networks may contribute to the maintenance of psychotic symptoms as integration with bottom-up sensory information is disrupted. Following from this view, one might argue that even if the striatal dopaminergic dysfunction is alleviated with antipsychotic medication, this would not necessarily suffice to reduce symptoms once they have been established if frontostriatal connectivity remains impaired. This two-hit model of treatment resistance would...
suggest that functional integration is more severely impaired in TRS compared to non-treatment-resistant patients. Consequently, antipsychotic treatment may effectively attenuate the striatal dopaminergic dysfunction, but in the absence of a normative regulation from the prefrontal cortex in TRS, symptoms could be perpetuated despite optimal treatment.

Unfortunately, both psychological and pharmacological interventions have yielded very limited clinical benefits in improving cognitive dysfunction in psychosis. A recently licensed antidepressant medication, vortioxetine, has data to support benefits on cognitive dysfunction, in addition to an effect on depressive symptoms. Vortioxetine is unusual in possessing multimodal action, both inhibiting serotonin transporters and also acting directly on specific serotonin receptors: 5-HT₁A (full agonism), 5-HT₁B (partial agonism) and antagonism at 5-HT₁D, 5-HT₃ and 5-HT₇. Although vortioxetine is a partial agonist at 5-HT₁B, long-term administration desensitizes the 5-HT₁B receptors. Interestingly, vortioxetine has been demonstrated to enhance frontal cortical activity and impact on wakefulness. In addition, a study by Katona and colleagues has demonstrated that vortioxetine may have an important wider role in improving cognitive dysfunction, impacting not only on learning and memory, but also on cognitive control and attention. They suggest that the improved cognitive performance might be explained by its effects on 5-HT₁A Receptor stimulation and 5-HT₃ Receptor antagonism involved in cognitive processes, leading to enhanced cortical glutamatergic neuronal firing.

In this case report we present three patients with TRS who could not be treated with clozapine due to severe side effects, but who were successfully treated with a combination of vortioxetine and lurasidone at the National Psychosis Service. This is a specialist inpatient ward located at the Bethlem Royal Hospital, London, which acts as a UK-wide tertiary referral facility for the treatment of patients with treatment-resistant psychotic disorders. We discuss possible mechanisms that may underlie the unique efficacy of this combination in TRS.

**Consent**

The patients all provided written informed consent for publication, which is available from the authors if required. The hospital does not require ethical approval to publish case reports.

**Patient 1**

Patient 1 is a 68-year-old married white British male with a diagnosis of TRS. He first presented with psychosis to psychiatric services in 1965 at age 17. Over the next four decades he was treated with a number of antipsychotic agents including sulpride, aripiprazole, haloperidol and olanzapine; all were at up to maximal British National Formulary recommended doses and a minimum of 12 weeks’ duration with compliance assured during inpatient episodes; he experienced a number of relapses over time. He did not achieve remission and was started on clozapine in 2002 (dose 400 mg daily). Following that, he was functional and relatively stable for 11 years, aside from some minor residual psychotic and anxiety symptoms.

His medical history at this time included ischaemic heart disease (IHD), cardiomyopathy with an ejection fraction of 35%, congestive heart failure (NYHA II) and bilateral pedal oedema. In 2014, following a decline in his cardiac function, his maintenance clozapine dose was reduced from 350 mg to 300 mg daily. Unfortunately, this was followed by a severe psychotic relapse characterized by prominent thought disorder, paranoid delusions, self-neglect and increasingly aggressive and challenging behaviour. His clozapine dose was increased back to 350 mg but his mental state continued to deteriorate and due to violence and aggression he was transferred to a psychiatric intensive care unit in March 2015.

In August 2016 he was admitted to the National Psychosis Unit, having been an inpatient for over 2 years. His symptoms at this time included persecutory delusional beliefs, obsessive-compulsive traits, anxiety, mood lability, prominent difficulties in concentration and memory and irritability with outbursts of aggression. Psychotropic medication on admission included lurasidone 111 mg (which he had been treated with for over 1 year), sertraline 100 mg and diazepam 6 mg daily. On admission, he scored 115 on the PANSS total score and 29/30 on the Mini Mental State Exam (MMSE). An MRI brain scan was within normal limits; blood tests on admission
were mostly within normal limits, except for a raised urea of 13.9 mmol/L (3.3–6.7) and an increased prolactin level of 894 mIU/L (100–410), attributed to lurasidone. The pharmacotherapeutic approaches considered included a trial of high-dose olanzapine, switching from sertraline to vortioxetine because of the added benefit in attention and cognitive flexibility, or adding either memantine or donepezil as adjuncts to aid cognition.

In August 2016 it was decided to increase his lurasidone dose to 148 mg daily. Sertraline was switched to adjunct vortioxetine 10 mg, which was gradually titrated to 20 mg over the next couple of weeks. By September 2016 there was noticeable improvement in symptoms, and by December 2016 he was in remission, scoring 44 on the PANSS total score. Pregabalin 25 mg BD was prescribed as an anxiolytic after stabilization on lurasidone and vortioxetine, and benzodiazepines were down-titrated and stopped. He was successfully discharged home in January 2017. Psychotropic medications on discharge included lurasidone 148 mg, vortioxetine 20 mg and pregabalin 25 mg BD. He described his wellbeing as 9 out of 10, compared to having been 1 out of 10 at admission. The family described his change as ‘miraculous, and that he had not been so well, even while being treated with clozapine’. Subsequent follow up confirmed a sustained functional and symptomatic recovery.

**Patient 2**

Patient 2 is a 31-year-old British woman with a diagnosis of TRS. She first presented to psychiatric services in 2002 (age 17) with flattened affect, inappropriate laughter, social withdrawal and functional decline. She was diagnosed with schizophrenia and over the next 10 years she was treated with various antipsychotics up to maximal British National Formulary recommended doses, including risperidone up to 8 mg, aripiprazole up to 30 mg and amisulpride up to 800 mg, to which she demonstrated a limited response.

Her medical history at this time included poorly controlled type I diabetes mellitus. Her blood sugar fluctuated from hypoglycaemia to hyperglycaemia and she was repeatedly admitted to medical wards for diabetic ketoacidosis.

Between 2009 and 2012 she presented with persistent positive psychotic symptoms: responding to auditory hallucinations, prominent thought disorder and inability to manage basic aspects of her personal care. This led to a psychiatric admission in June 2015 and clozapine was commenced in July 2015. There was no significant improvement in her mental state on clozapine, and over the next 6 months various augmentation strategies were attempted without success. These included amisulpride up to 800 mg daily, aripiprazole up to 20 mg daily and lurasidone 74 mg daily – all provided no significant benefit.

She was admitted to the National Psychosis Unit in October 2016 having been an inpatient for 16 months with persistent psychotic symptoms. Psychotropic medications on admission included clozapine 350 mg and lurasidone 74 mg daily (she had been treated with this for over 6 months). She was also prescribed insulin and pioglitazone to manage her diabetes. On admission she scored 110 on the PANSS total score and was unable to attend sufficiently to complete the MMSE. MRI of the brain was normal. Blood results at admission were within normal limits except for a raised HbA1c 9.5% (4.1–6.0), random glucose 22.4 mmol/L (3.0–6.0), ALP 209 IU/L (30–130), cholesterol 5.4 mmol/L (1.0–5.0) and lipid ratio 4.5. Her clozapine level on admission was 0.30 mg/L.

In early November 2016 her clozapine dose was increased to 375 mg daily, with a subsequent serum level of 0.66 mg/L. Her diabetes remained extremely difficult to control and she had a medical admission for diabetic ketoacidosis. By mid-December 2016 the increased clozapine dose had conferred no additional clinical improvement. Given the difficulty controlling her diabetes and the lack of any clear benefit from clozapine treatment for over a year, clozapine was stopped and instead lurasidone was increased to 111 mg. At the end of December 2016 vortioxetine 10 mg was commenced as a trial adjunct to enhance her cognition and attention. Within a few weeks of initiating vortioxetine, there was a remarkable improvement in all domains. She was more engaging, appeared brighter in mood, less distressed by psychotic symptoms and was able to attend to her self-care and acknowledge the change since admission, saying that her thinking felt clear and that voices were bothering her less. By January 2017 she scored 60 on the PANSS total score and 27/30 on MMSE. By February 2017 her diabetic control had improved; pioglitazone had been stopped, she required lower doses of insulin and her HbA1c had come down from 9.5% to 7.9%. By April 2017, she had maintained
her improvement on lurasidone 111mg and vortioxetine 10 mg and was awaiting discharge.

**Patient 3**

Patient 3 is a 44-year-old single white British woman. She first presented to psychiatric services in 1987 (age 15) with self-harming behaviour, mood instability and aggression. She was diagnosed with emotionally unstable personality disorder. In 1990 she was detained under the Mental Health Act for over a year and diagnosed as having a psychotic illness.

In 2009 she was admitted to hospital with a diagnosis of schizophrenia and personality disorder, with symptoms including auditory hallucinations, impulsivity, intrusive thoughts, assaultive behaviour, suicide attempts and emotional dysregulation. She was trialled on haloperidol up to 20 mg daily and carbamazepine 800 mg daily with limited benefit. In 2009 this was switched to clozapine (with therapeutic serum levels), leading to an initial reduction in her psychotic symptoms, with a long relapse necessitating clozapine augmentation strategies including sodium valproate 1800 mg daily (2013–2015), topiramate 250 mg daily (2014–2016) and paroxetine up to 40 mg daily (2014–2015) with little success. In March 2015 she was found to have atrial fibrillation and as a consequence clozapine was stopped on a cardiologist’s advice. She was managed without any antipsychotics due to concerns about her cardiac status. After stopping clozapine, a significant deterioration in her mental state was noted. She was responding to external stimuli, laughing to herself, had minimal interactions with others and over time became near mute, but when speaking was noted to be thought-disordered. She continued to be doubly incontinent, had episodes of aggression and a lack of volition. She needed prompting with all aspects of personal care, eating and drinking, and she lost 30 kg of weight.

She was admitted to the National Psychosis Unit in December 2016, having been an inpatient since 2009 with persistent psychotic symptoms, more recently a catatonic presentation and mute for 18 months. Psychotropic medication on admission included topiramate 125 mg BD and clonazepam 0.5 mg BD. There were prominent negative psychotic symptoms, including lack of volition and a flat affect. She rarely got out of bed, continuing to be doubly incontinent. She was mute but some inappropriate laughter was noted. On admission she scored 117 on the PANSS total score and she was unable to complete an MMSE. She scored 17 on the Bush-Frances Catatonia Rating Scale. Bloods and ECG on admission were normal.

Initially clonazepam was changed to lorazepam 2 mg QDS because of suspected catatonia. In mid-December 2016 she was commenced on lurasidone 74 mg which was titrated up to 111 mg by the end of December 2016. Topiramate was slowly reduced and stopped. After about a month on the ward an improvement in her mental state was noted, with her gradually becoming more responsive and communicative. She began to get out of bed and engage in conversation with patients and carers. She described low mood and in February 2017 vortioxetine 10 mg was started for an empirical trial of antidepressant and to enhance cognition. Within a few weeks she was described as bright and happy in mood, initiating conversation and pleasant on interaction. Her incontinence improved and physical medication for that was stopped. Lorazepam was replaced with diazepam with a plan for a gradual decrease and discontinuation. By February 2017 she scored 57 on the PANSS total score and by March 2017 her MMSE had increased to 22/30. She currently reports feeling ‘a lot better’ and describes that her quality of life has increased from 0 out of 10 on admission to 7 out of 10 currently treated with lurasidone 111 mg and vortioxetine 10 mg.

**Discussion**

In these three cases of severe TRS, a strikingly clear and marked clinical improvement in psychotic symptoms and cognition, reflected mostly in their social interactions, was observed when treated with a combination of vortioxetine and lurasidone. This suggests that the novel combination of vortioxetine and lurasidone may be a treatment option to consider when clozapine is...
indicated, but not able to be utilized due to concerns about adverse side effects or tolerability. These patients are unusual in having been previously treated with clozapine and showing an initial moderate response in two cases, with the response not being sustained in one of these; in the third case it failed to benefit the patient, with only a minimal response. The routine clinical observation on discontinuation of clozapine is of a severe rebound psychosis and exacerbation of symptoms; on the contrary, these cases show positive effects on this novel combination of medication. Two of the three patients had been previously receiving treatment with lurasidone without significant impact on their psychotic symptoms, indicating that the addition of the vortioxetine was most likely to be the most significant change. There is no published literature, but a single published abstract of lurasidone in treatment-refractory schizophrenia suggested some potential benefit in areas of cognition and psychotic symptoms. Two of the patients had been treated with SSRI medication in the past, without significant impact on their symptoms. This suggests that the psychopharmacological profile of vortioxetine, specifically the pro-cognitive effect, may be the key factor in their improvement. Interestingly, the actions of long-term vortioxetine administration overlaps with several actions of clozapine (Table 1).

There has been longstanding interest in the role of serotonin in schizophrenia, heightened by the observation that clozapine possessed a higher affinity at the 5-HT2A receptor sites compared to the response not being sustained in one of these; in the third case it failed to benefit the patient, with only a minimal response. The routine clinical observation on discontinuation of clozapine is of a severe rebound psychosis and exacerbation of symptoms; on the contrary, these cases show positive effects on this novel combination of medication. Two of the three patients had been previously receiving treatment with lurasidone without significant impact on their psychotic symptoms, indicating that the addition of the vortioxetine was most likely to be the most significant change. There is no published literature, but a single published abstract of lurasidone in treatment-refractory schizophrenia suggested some potential benefit in areas of cognition and psychotic symptoms. Two of the patients had been treated with SSRI medication in the past, without significant impact on their symptoms. This suggests that the psychopharmacological profile of vortioxetine, specifically the pro-cognitive effect, may be the key factor in their improvement. Interestingly, the actions of long-term vortioxetine administration overlaps with several actions of clozapine (Table 1).

These cases provide preliminary support for the proposal that TRS is characterized by a two-hit model, where conventional antipsychotic treatment may effectively attenuate the striatal dopaminergic dysfunction, but in the absence of a normative response from the prefrontal cortex in TRS, symptoms could be perpetuated despite optimal treatment. Here, a pro-cognitive intervention based on the serotonergic system has demonstrated positive effects on both cognition and psychotic symptoms. While speculative, it has support from the literature. It is well recognized that serotonin levels in the brain are regulated by the serotonin reuptake transporter (SERT) at the presynaptic nerve terminal. Both 5-HT1B and 5-HT1D receptors are presynaptic autoreceptors involved in negative feedback loops for serotonergic neurons. When stimulated, these receptors inhibit 5-HT release from neurons. By desensitizing 5-HT1B receptors and antagonizing 5-HT1D receptors, vortioxetine disinhibits 5-HT release. This effect, synergistically combined with blocking SERT, leads to a larger increase in 5-HT levels than blocking SERT alone, although the increase is still prevented from reaching dangerous levels by monoamine oxidase (MAO) activity. Clinically, the increase in 5-HT translates into antidepressant effect.

This property of vortioxetine may be beneficial in psychotic patients with negative symptoms such as low mood. Aside from regulating 5-HT release from serotonergic neurons, 5-HT1B receptors are also found as heteroreceptors on non-serotonergic neurons. In this context, 5-HT1B receptors inhibit the release of other neurotransmitters such as acetylcholine in the hippocampus, dopamine in the striatum, GABA and glutamate in widespread projections across the brain.

This is interesting because differential glutamatergic changes have been observed in the anterior cingulate cortex of the frontal cortex in TRS. By desensitizing 5-HT1B receptors, vortioxetine has the potential to modulate release of these other neurotransmitters across the brain. This may be one mechanism whereby vortioxetine enhances cognitive function.

Vortioxetine also acts as a high-affinity antagonist at 5-HT1 receptors, an action which is shared with clozapine (Table 1). 5-HT1A receptors are found as excitatory heteroreceptors on GABAergic interneurons in the prefrontal cortex and amygdala. There they facilitate GABA release, forming part of a negative feedback circuit which inhibits 5-HT release from pyramidal cells in the midbrain raphe. Antagonism of 5-HT3 receptors by vortioxetine disinhibits this negative feedback loop, increasing 5-HT release from pyramidal cells in the midbrain raphe and enhancing hippocampal long-term potentiation and frequency of hippocampal theta rhythm. Aside from regulating 5-HT release in the midbrain and hippocampal long-term potentiation, 5-HT3 receptors also regulate release of noradrenaline, acetylcholine and dopamine throughout the brain. In summary, vortioxetine’s antagonism of 5-HT3 receptors on GABAergic interneurons leads to increased 5-HT, noradrenaline and acetylcholine levels and enhanced hippocampal memory formation – potentially enhancing...
vortioxetine’s antidepressant and pro-cognitive effects.

It is entirely possible that the improvements seen in these cases are due to the synergistic effects of the combination of vortioxetine and lurasidone. Lurasidone is a relatively new antipsychotic which, similar to clozapine, has antagonistic action at D2 and 5-HT2A receptors; however, it also has high affinity for 5-HT1A (partial agonism), 5-HT3 (antagonism) and norepinephrine α2C receptors17 – receptors implicated in enhancing cognition and mood and reducing negative symptoms of schizophrenia.25 It is possible that the clinical improvement observed in our cases when vortioxetine is added to lurasidone may be mediated via their combined effects on D2, 5-HT1A, 5-HT1D or 5-HT3 receptors (and potentially also by the effect of full agonism at 5-HT1A).

There are the obvious limitations of case report data, with the presence of many uncontrolled

| Receptor | Clozapine | Vortioxetine | Lurasidone |
|----------|-----------|--------------|------------|
| 5-HT1A   | +         | Partial agonist | +          | Agonist |
| 5-HT1B   | +         | Antagonist    | +          | Partial agonist |
| 5-HT1D   | +         | Antagonist    | +          | Antagonist |
| 5-HT2A   | +++       | Antagonist    | +++        | Antagonist |
| 5-HT2B   | ++        | Antagonist    |            |            |
| 5-HT2C   | +         | Antagonist    |            |            |
| 5-HT3    | +         | Antagonist    | +++        | Antagonist |
| 5-HT4    | ++        | Antagonist    |            |            |
| 5-HT6    | ++        | Antagonist    |            |            |
| SERT     | +         | Antagonist    | +++        | Inhibition |
| D1       | +         | Antagonist    |            |            |
| D2       | ++        | Antagonist    | +++        | Antagonist |
| D3       | +         | Antagonist    | +          | Antagonist |
| D4       | ++        | Antagonist    | +          | Antagonist |
| D5       | +         | Antagonist    |            |            |
| H1       | +++       | Antagonist    |            |            |
| M1       | ++        | Partial agonist | +          |            |
| M2       | +         | Partial agonist | +          |            |
| M3       | +         | Antagonist    |            |            |
| M4       | +         | Partial agonist | +          |            |
| M5       | ++        | Partial agonist | +          |            |
| α1A      | +++       | Antagonist    |            |            |
| α1B      | +         | Antagonist    |            |            |
| α2A      | +         | Antagonist    | +          | Antagonist |
| α2B      | +         | Antagonist    | +          | Antagonist |
| α2C      | +         | Antagonist    | +          | Antagonist |

Note: Affinity expressed as Ki (nM). + >100 Ki (nM), ++ 10–100 Ki (nM), +++ <10 Ki (nM). SERT, serotonin reuptake transporter.
variables which could influence outcomes in these complex patients. We made a decision not to withdraw the adjunct medication to test response, as this was considered to be unethical. However, the patients had a consistent baseline of persistent symptoms and poor functioning in an inpatient setting over at least the period of a year, with assured compliance with medication. The assessments were carried out using standard tools by experienced staff, although not blinded to the treatment. The changes observed in the patients were sufficiently striking, that they were noted spontaneously by the patients and their carers, who were often unaware of the specific medication changes being implemented.

The pro-cognitive treatment approach used in these patients in this naturalistic case report may be of value when clozapine is not feasible or tolerated; and complements other experimental approaches that aim to enhance cognitive control through brain stimulation or using neurofeedback techniques. We believe that these novel clinical observations warrant further assessment in a prospective randomized controlled clinical trial – both to assess the benefit of adjunct vortioxetine and to clarify if this beneficial effect is unique to the combination with lurasidone.

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Conflict of interest statement
The authors declare that there is no conflict of interest.

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