

Methadone augmentation of clozapine in treatment-resistant schizophrenia without opiates addiction: a case report

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Summary

Guaiana G, Salvioli C, Mariconda G. Methadone augmentation of clozapine in treatment-resistant schizophrenia without opiates addiction: a case report. Schweiz Arch Neurol Psychiatr. 2009;160:122–3.

We present a single 26-year-old patient with a long-standing diagnosis of disorganised schizophrenia (without heroin dependence) which was treatment resistant. We treated him with a combination of clozapine and methadone, and we saw an improvement after one week of treatment.

Keywords: schizophrenia; methadone; clozapine; glutamate; dopamine; NMDA receptor

It is estimated that 20–45% of patients with schizophrenia do not respond to treatment [1]. Clozapine has been considered the treatment of choice in those treatment-resistant patients [1]. Unfortunately, only 30–60% of people treated with clozapine respond to this medication [2]. It is possible to augment clozapine with another medication, but robust evidence is still lacking [3].

We present a single 26-year-old patient with a long-standing diagnosis of disorganised schizophrenia, who was admitted to our ward after a relapse. He has a history of schizophrenia since the age of 17. Different treatments had been tried in the past, yielding only transient and unstable improvement in his symptoms. He has a current history of cannabis abuse, with occasional use of heroin, cocaine and hallucinogens up to some years ago. On admission, he experienced severe command hallucinations, affective flattening, psy-

chomotor retardation, with sudden bursts of agitation and odd behaviour. We were then forced to restrain him due to the high danger he posed to himself. We managed to perform routine blood tests as soon as he was admitted, including regular full blood counts, electrolytes and liver-function tests, which gave no abnormal result. His brief psychiatric rating scale (BPRS) score on admission was 132. He had a pharmacological therapy with clozapine 900 mg/day, haloperidol 4 mg/day and lorazepam 7.5 mg/day. After a week, he continued to experience psychotic symptoms. We decided to change his treatment, reducing his clozapine to 400 mg/day, stopping all other medication and introducing methadone at an initial dose of 15 mg/day. After two weeks, we saw a change in his psychomotor activity and thought organisation, in that he was calmer and more organised. After a further week, delusional ideas disappeared as well as command hallucinations and odd behaviour. We could unrestrain him as he posed no risk for himself. His BPRS score, after about three weeks on methadone augmentation, was 68. No additional medication was used over these three weeks on methadone. ECGs made before and after administration of methadone did not show any abnormality. He remained on clozapine 400 mg/day and methadone 15 mg/day only.

To our knowledge, this is the first report of a patient with schizophrenia, without heroin dependence, successfully treated with methadone augmentation. We postulate a possible mechanism that might explain our patient's response. It is possible that methadone could have acted synergically with clozapine at glutamate NMDA receptor (NMDAR) site. Clozapine and methadone are, respectively, agonist and antagonists at NMDAR site [4, 5]. We think that the interaction of clozapine and methadone at NMDAR site might explain our patient's improvement, according to Shim and colleagues' hypothesis [4]. They hypothesise that an ideal set-point of NMDAR stimulation is needed to achieve symptomatic remission. Our hypothesis is that methadone (an NMDAR antagonist) in association with clozapine (NMDAR agonist)

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could have reduced NMDAR stimulation up to the ideal set-point, making symptomatic remission possible. This hypothesis needs confirmation from preclinical and clinical studies.

References

- 1 Conley RR, Buchanan RW. Evaluation of treatment-resistant schizophrenia. *Schizophr Bull.* 1997;23:663–74.
- 2 Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry.* 1988;45:789–96.
- 3 Kontaxakis VP, Ferentinos PP, Havaki-Kontaxaki BJ, Paplos KG, Roukas DK, Christodoulou GN. Case studies of adjunctive agents in clozapine-resistant schizophrenic patients. *Clin Neuropharmacol.* 2005;28:50–3.
- 4 Shim SS, Hammonds MD, Kee BS. Potentiation of the NMDA receptor in the treatment of schizophrenia: focused on the glycine site. *Eur Arch Clin Neurosci.* 2008;258:16–27.
- 5 Manfredi PL, Hiude RW. Prescribing methadone, a unique analgesic. *J Supp Onc.* 2003;1:216–20.