CASE REPORT

Directly observed therapy for clozapine with concomitant methadone prescription: a method for improving adherence and outcome

Nicholas Tze Ping Pang,¹ Mohd Fadzli Mohamad Isa,² Vikram Suarn Singh,³ Ruziana Masiran⁴

¹Department of Psychiatry, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia

²Department of Psychiatry and Mental Health, Hospital Kuala Lumpur, Kuala Lumpur, Wilayah Persekutuan, Malaysia

³Department of Psychiatry, Pusat Perubatan Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia

⁴Department of Psychiatry, University Putra Malaysia, Serdang, Selangor, Malaysia

Correspondence to
Dr Ruziana Masiran,
ruziana78m@yahoo.com

Accepted 10 July 2017

SUMMARY

A young male presented with many years of delusions and hallucinations, with concurrent heroin use and subsequent amphetamine uses. There were no depressive or manic symptoms and psychotic symptoms prior to the amphetamine use. After the trials of two atypical antipsychotics and later clozapine due to treatment resistance, adherence and functionality were poor and there was still persistent drug use. As a result, a long acting injectable adjunct was commenced, but only minimal effects were observed. However after initiation of directly observed treatment of clozapine with methadone, there has been functional and clinical response and drug use has ceased.

BACKGROUND

Directly observed treatment (DOT) has been established as a treatment modality in tuberculosis and is recommended by multiple international guidelines. However, its use has not been widely adopted in mental health practice yet. In the field of addiction psychiatry, DOT is currently being practised regularly with methadone. It is looking likely that this treatment methodology can be extended to antipsychotics, potentially in those with dual diagnosis.

CASE PRESENTATION

We describe the case of a 43-year-old single Asian male whose first contact with psychiatry services was in July 2002. He exhibited abnormal behaviours, including demanding to meet the country's Prime Minister after getting a message from God. This was associated with an auditory hallucination commanding him to give this message. He also had persecutory delusions towards his foster parents. During that admission, his urine was only positive for morphine. There were no clear depressive, manic or neurotic symptoms at that time.

He denied any amphetamine or cannabis use prior to his first contact which was corroborated by urine toxicology. In terms of drug use, he had been a heavy smoker and has been using daily heroin since his teenage years. There is a history of casual alcohol consumption and cannabis use in the past. He only started using methamphetamines in 2010 (8 years after his psychotic symptoms began) during his employment as a security guard in order to stay

awake. In addition, he has had multiple forensic involvement for drug possessions. Following the onset of psychosis, he has also taken the methamphetamines to self-medicate and relief himself off the psychotic symptoms.

He is hepatitis C positive, diagnosed in 2010. His birth and development history were uneventful. There is no family history of mental illness, but he was adopted at the age of three hence had difficulty forming attachments with both adoptive parents. There were truancy issues throughout secondary school. Due to substance use and poorly controlled illness, he has subsequently had multiple changes of employment and has been unable to sustain a relationship.

Mental state examination revealed a well-groomed Asian male with relevant and coherent speech. He was euthymic and there were no delusions; however, there were minimal residual elemental auditory hallucinations. Physical examination was unremarkable.

INVESTIGATIONS

A battery of investigations, including full blood counts, thyroid, liver and renal function tests, were normal.

DIFFERENTIAL DIAGNOSIS

His primary diagnosis was schizophrenia; multiple episodes, currently in partial remission as per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. This is due to the presence of hallucinations and delusions, the primacy of symptoms despite remission of amphetamine use, and the functional impairment. Otherwise according to DSM-5 criteria, he qualified for various other substance use disorders. This include opioid use disorder, in early remission, on maintenance therapy; amphetamine-type stimulant use disorder, in early remission; nicotine use disorder, moderate.

TREATMENT

He was initially treated with an adequate dose and duration of olanzapine and risperidone (two different antipsychotics) however symptoms persisted. At the same time, methadone maintenance therapy was initiated to which he responded well as heroin use ceased. In terms of the

CrossMark

To cite: Pang NTP, Mohamad Isa MF, Suarn Singh V, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-221048

methamphetamine use, he was given motivational interviewing revealing he was in pre-contemplative stage. However, it was recognised that treatment of his psychotic symptoms would lead to resolution of the methamphetamine use.

On starting clozapine however, there were issues with adherence due to his erratic lifestyle; hence, depot fluphenazine monthly was started, but he was still not responding fully to clozapine. He required 14 admissions from his first diagnosis in 2002 up to May 2016, with admissions to a mental health institution in between. There was a possibility of methamphetamine-induced psychosis during some of the admissions. However, urine for drugs would usually test negative for methamphetamine as the use was sparing and sporadic only. Motivational interviewing for methamphetamine use throughout suggested he was still in the contemplative stage.

OUTCOME AND FOLLOW-UP

Due to incomplete response of positive symptoms to clozapine, poor adherence and continued drug-seeking behaviour to self-medicate as a consequence, a decision was made to administer his clozapine with his methadone daily as DOT on discharge in May 2016. Since then adherence has been complete, there has been a marked reduction in positive symptoms, and he has not experienced any relapses or required any admissions. After DOT was started, his substance use reduced and subsequently stopped and his functioning has improved too. Urine toxicology has been negative since DOT was started. He has also stopped methamphetamine use after his clozapine was given as DOT as there was no more need to self-medicate.

DISCUSSION

The DOT has been used for tuberculosis as an internationally recommended strategy. Regular uninterrupted supply of a standardised chemotherapy treatment regimen and administration under the supervision of a health worker or trained close relative who watches and records the patient swallowing the correct dose of drugs are the key points.¹ This has led to staggering improvements in TB control in many countries.² Contrary to common wisdom, DOT actually costs less than self-administered therapy for TB.³

Schizophrenia, though rare (with a prevalence of close to 1%),⁴ wreaks its disproportionate effects twofold. First, its onset is typically in the twenties, affecting individuals at the peak of their productive years.⁴ Low-income and middle-income countries (LAMICs), by virtue of still having a 'pyramid'-shaped population distribution due to the high reproductive rates, are disproportionately affected. At the same time, poor mental health literacy secondary to socioeconomic inequality results in many cases presenting much later on in illness with a longer duration of untreated psychosis,⁵ making them more treatment resistant at first contact. This situation is not restricted to LAMICs—schizophrenia is a disease that predominantly affects the urban poor also, of which the developed world has a lot of in ghettos and downtowns. Be it in the Paris or in Peshawar, New York or in Nairobi, restricted access to resources, poverty and social disadvantage still result in schizophrenia causing the unnecessary morbidity that it does.

Therein lies the possibility of using DOT as a strategy to accomplish this. Various strategies that are similar to DOT, including guardianship networks⁶ and community services,⁷ have been shown to demonstrate efficacy in improving treatment adherence. This model was employed in a 2-year trial of STOPS (supervised treatment for outpatients with schizophrenia) versus

treatment as usual, where the participants in the STOPS group had better adherence and significant improvements in symptoms and functioning.⁸ This involved appointment of key workers in the family with intense psychoeducation and training given in order to reduce stigma.

There have been other issues regarding DOT-type scenarios, for example, poor training of family or healthcare workers and need to adjust medication doses in schizophrenia.⁹ However, the same issues plague DOT of TB but have not adversely affected its efficacy in TB. The main issue is the provision of free medications that is a cornerstone of DOT. The case illustrated had medications provided by the national healthcare system, but this advantage might not be readily available in some centres or countries.

Dual diagnosis complicates the treatment of primary psychiatric disorders. Since 60% of patients are already non-adherent in schizophrenia,¹⁰ this figure will probably become higher in dual diagnosis due to the erratic and chaotic lifestyles employed. It turns into a vicious cycle; substance use increases proportionately to schizophrenia severity in attempts to self-medicate, or to act out against perceived failure of authority (medical care). In instances where DOT (methadone) has already been started, it can be advantageous to add the antipsychotic to that DOT regime as long as there are no contraindications. The combination is able to control the primary illness and reduces both illness symptoms and functional impairment which might push the patient further into the direction of increased drug taking. At the same time, DOT can improve the therapeutic alliance between patients and healthcare workers due to regular contact which in itself is an independent predictor of response.¹¹

Learning points

- Dual diagnosis creates complications in terms of management of both psychosis and substance; however, it also creates unexpected opportunities in terms of creative methods for enhancing medication adherence.
- Directly observed treatment can be a valuable strategy both in high-income countries and low-income and middle-income countries for improving adherence, increasing therapeutic alliance, and reducing functional impairment and drug use in dual diagnosis.

Contributors NTPP, MFMI and VSS were involved in the clinical management of the case. NTPP and RM drafted and finalised the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 World Health Organization. What is DOTS? A guide to understanding the WHO-recommended TB control strategy known as DOTS. 1999. http://whqlibdoc.who.int/hq/1999/WHO_CDS_CPC_TB_99.270.pdf
- 2 Squire SB, Tang S. How much of China's success in tuberculosis control is really due to DOTS? *Lancet* 2004;364:391–2.
- 3 Moore RD, Chaulk CP, Griffiths R, et al. Cost-effectiveness of directly observed versus self-administered therapy for tuberculosis. *Am J Respir Crit Care Med* 1996;154:1013–9.
- 4 Saha S, Chant D, Welham J, et al. A systematic review of the prevalence of schizophrenia. *PLoS Med* 2005;2:e141.
- 5 Farooq S, Large M, Nielssen O, et al. The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: a systematic review and meta analysis. *Schizophr Res* 2009;109:15–23.

- 6 Qui F, Lu S. Guardianship networks for rural psychiatric patients. *Br J Psychiatry* 1994;165:114–20.
- 7 Srinivasa Murthy R, Kishore Kumar KV, Chisholm D, *et al.* Community outreach for untreated schizophrenia in rural India: a follow-up study of symptoms, disability, family burden and costs. *Psychol Med* 2005;35:341–51.
- 8 Farooq S, Nazar Z, Irfan M, *et al.* Schizophrenia medication adherence in a resource-poor setting: randomised controlled trial of supervised treatment in out-patients for schizophrenia (STOPS). *Br J Psychiatry* 2011;199:467–72.
- 9 Souza R, Yasuda S, Cristofani S. Treating schizophrenia with DOTS in developing countries: one size does not fit all. *PLoS Med* 2007;4:e281.
- 10 Kampman O, Lehtinen K. Compliance in psychoses. *Acta Psychiatr Scand* 1999;100:167–75.
- 11 Lacro JP, Dunn LB, Dolder CR, *et al.* Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry* 2002;63:892–909.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow