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Rabbit syndrome treated with olanzapine

We wish to share with you our experience in treating a person with schizophrenia who developed rabbit syndrome. Rabbit syndrome, characterised by rapid, rhythmic orofacial movements, often accompanied by lip sounds (Schwartz *et al*, 1995) is considered one of four tardive dyskinesia (TD) variants, all of which are extrapyramidal side-effects of long-term neuroleptic treatment (Inada *et al*, 1991). The incidence of rabbit syndrome among TD variants is about 2.4% (Wada & Yamaguchi, 1992), with a mean prevalence of 15–20% among neuroleptic-treated patients in general (Baldessarini, 1988) and 9.9% in psychiatric hospital populations. Olanzapine is hereby suggested as a possible solution for alleviating rabbit syndrome without risking the emergence of extrapyramidal side-effects and simultaneously combating schizophrenic symptoms.

A 28-year-old single woman, suffering from schizophrenia for nine years, had been treated by depot injections of zuclopenthixol (200 mg every fortnight) and with biperiden (4 mg/day) since 1995. Her mental state deteriorated and she was hospitalised in an acute psychotic state, suffering from paranoid delusions. Signs of typical rabbit syndrome were evident.

In seeking out an appropriate treatment strategy for her psychotic state and the rabbit syndrome (which did not seem to respond to biperiden), it was decided to stop administration of zuclopenthixol and to initiate olanzapine, starting at 5 mg/day and reaching maximal dosage (10 mg/day). Within 2–3 weeks, not only had her psychotic symptoms disappeared, but improvement was also observed in her rabbit syndrome. Her Abnormal Involuntary Movement Scale (AIMS, Wojcik *et al*, 1980) score dropped from 14 to 8. After 25 days of hospitalisation, she was released into community care and continued to receive olanzapine (10 mg/day). Follow-up, a year later, found her to be in remission from the psychosis, with no signs of rabbit syndrome, under olanzapine treatment.

It has been postulated that the underlying mechanism of rabbit syndrome is supersensitivity of dopamine receptors, possibly due to an underlying predisposition. It has also been suggested that rabbit syndrome is a result of multiple system atrophy (Nishiyama *et al*, 1993). The most prominent, albeit controversial, treatment agents for rabbit syndrome are benzhexol and biperiden. We were anxious to avoid aggravation or uncovering of TD by the addition of anticholinergic agents. Olanzapine displays high affinity for type 2 serotonin ($5\text{-}HT_2$) receptors and, although the activity ratio between $5\text{-}HT_2$ and type 2 dopamine (D_2) receptors is slightly lower than for clozapine, it is still about twice as active at $5\text{-}HT_2$ than at D_2 receptors. Hence, olanzapine is less likely to be associated with TD, and its application in preventing or ameliorating rabbit syndrome seemed appropriate (O'Brien & Barber, 1998).

This case demonstrates the possible usefulness of olanzapine as a mono-drug treatment strategy for dealing with rabbit syndrome triggered by typical neuroleptics and simultaneously treating psychotic symptoms.

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Serotonin transporters in ecstasy users

Semple *et al* (1999) report a reduction *in vivo* of ^{123}I-labelled 2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT) uptake in the cerebral cortex of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') users. They interpret this observation to be an indication of a decrease in serotonin transporters in the cortex of MDMA users. However, there are serious methodological concerns with this interpretation of their data.

It has been demonstrated that the radioligand [^{123}I]β-CIT binds with high affinity to dopamine, serotonin and noradrenaline transporters in human brain (Farde *et al*, 1994; Laruelle *et al*, 1994). In the case of the serotonin transporter, *in vivo* displacement of β-CIT binding by selective serotonin reuptake inhibitors (SSRIs) has established that specific (displaceable) binding occurs in brainstem and thalamus (Laruelle *et al*, 1993; Pirker *et al*, 1995; Tauscher *et al*, 1999). However, this is not true for the cerebral cortex. Indeed, Laruelle *et al* (1993) observed that [^{123}I]β-CIT uptake in cortical areas was unaffected by citalopram administration in non-human primates. Similarly, recent SSRI displacement studies of [^{11}C]McN-5652, a selective serotonin transporter radioligand for positron emission tomography (PET) imaging, failed to observe specific binding in the cerebral cortex (Parsey *et al*, 1999). The lack of evidence for specific binding to serotonin transporters in the cerebral cortex *in vivo* is not surprising when one considers the paucity of these transporters in primate cortex (Jagust *et al*, 1996). We are aware of only a single report of apparent displacement of β-CIT by citalopram in primate cortex:

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a PET study of [^{11}C]β-CIT uptake in two cynomolgus monkeys (Farde *et al*, 1994). However, the shape and time-scale of the binding curves for the cynomolgus monkeys are strikingly different from those observed in other non-human primate species (Laruelle *et al*, 1993) and in humans (Farde *et al*, 1994; Laruelle *et al*, 1994; Pirker *et al*, 1995). This discrepancy is particularly pronounced for the cortical curve, and one wonders to what extent these data may be relevant to human studies. Be that as it may, the bulk of the evidence indicates that serotonin transporters are present in sufficient density to be measured reliably with [^{123}I]β-CIT only in the thalamus and brainstem, and not the cerebral cortex. The region of choice is the raphe area of the brainstem because the thalamus may have a substantial admixture of noradrenaline transporters (Farde *et al*, 1994) and because it is difficult to avoid scattered radiation from the much greater accumulation of activity in the striatum in a thalamic region of interest. We have found this to be true in our studies of serotonin transporters with [^{123}I]β-CIT, and we have observed that uptake in cortical regions does not differ significantly from the non-displaceable (non-specific) uptake seen in the cerebellum (Heinz *et al*, 1998). At extended times (>4 hours post-injection in humans), when specific binding to serotonin transporters in the brainstem approaches a near-equilibrium plateau and non-specific uptake continues to washout throughout the brain, it becomes clear that cortical uptake is 'tracking' that of the cerebellum.

This latter point raises a further methodological concern. Semple *et al* (1999) imaged [^{123}I]β-CIT uptake at 90 minutes post-injection hoping to assess radioligand binding to serotonin transporters. However, near-equilibrium conditions for β-CIT at serotonin transporters are not established in human brain earlier than about four hours post-injection (Laruelle *et al*, 1994; Pirker *et al*, 1995). Once near-equilibrium has been established, [^{123}I]β-CIT binding to serotonin transporters in the brainstem is quite stable and persists well into the following day (Laruelle *et al*, 1994; Pirker *et al*, 1995). Measurements at extended times of [^{123}I]β-CIT activity in human brainstem (following decay correction and subtraction of non-specific uptake) are simply proportional to the density of serotonin transporters (Laruelle *et al*, 1994). Unfortunately, this is not the case for the measurements of Semple *et al* (1999) at 90 minutes post-injection. At times this early, the system is not near equilibrium, and factors related to radioligand delivery and washout, rather than transporter binding *per se*, play a prevalent role in determining the appearance of [^{123}I]β-CIT images. Thus, it seems likely that factors such as blood flow, blood–brain barrier integrity, tissue permeability, etc. have confounded the cortical measurements that Semple *et al* (1999) have assumed to be due to serotonin transporters.

In summary, although Semple *et al* (1999) report an interesting reduction in β-CIT uptake in the cerebral cortex of MDMA users, there is no scientifically sound basis for ascribing this observation to a decrease in cortical serotonin transporters.

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Authors' reply: By necessity, the discussion of methodological constraints had to be very concise in the published version of our paper (it was more detailed and included some of the arguments raised by Heinz & Jones in the originally submitted manuscript). We are therefore glad to have this opportunity to respond to the constructive comments of Heinz & Jones. They essentially make two claims: that β-CIT does not reliably label cortical serotonin transporters, so that our observed group difference must be due to an alternative mechanism; and at 90 minutes after tracer injection there is a significant admixture of other effects, such as blood flow, blood–brain barrier integrity and tissue permeability, with the same result.

The first claim is supported by some, but not all, displacement studies with SSRIs in monkeys, but inter-species comparisons of brain measures have to be judged with reserve, as Heinz & Jones point out. They also cite a very recently published abstract of a study in six humans, using an alternative (PET-) ligand. We look forward to the full paper; if the initially reported claim survives peer review, it may certainly call into question our interpretation. Moreover, it will specifically weaken the McCann *et al* (1998) paper, whose authors used the same PET tracer and found cortical reductions in serotonin transporter labelling. The design of our study was based on Kuikka *et al*'s (1995) original report. They examined relatively large numbers of healthy volunteers (28) and patients (9) at one and two hours after injection of β-CIT. They reported significant tracer washout with 20 mg citalopram from medial prefrontal cortex (Brodmann's area 12) in 25 subjects, 1–2 hours after injection. They also found significant specific binding of serotonin transporters in occipital cortex. Both are regions that showed activity reductions in our MDMA users. They further described reduced medial prefrontal cortex β-CIT activity at 1 hour in five (alcoholic) patients compared with controls, in the absence of perfusion differences measured with the single photon emission computed tomography (SPECT) ligand ^{99m}Tc–ethyl cysteinate dimer.

The second (weaker) claim made by Heinz & Jones is correct in the sense that group differences in β-CIT binding at 90 minutes do not necessarily reflect a difference in serotonin transporter binding. However, in the absence of *a priori* hypotheses about generalised cell loss, reductions in blood flow, increased blood–brain barrier integrity or reduced tissue permeability,

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