cumulative over the course of development. This further suggests that the presentation of psychosis represents a culmination of an ongoing interaction between an individual and his/her environment. This remains the only reasonable explanation for the variation in incidence rates, particularly those reported for migrant populations in Britain and Europe (Hutchinson & Haasen, 2004). Interactions between perceptions of self, cognitive processes and the features of a modern urban environment underlie social development. The relative weighting of vulnerability and resilience factors is a function of this interaction and must in turn be affected by wider social issues such as racism, socioeconomic opportunity and perceived social isolation. There is also the generational transfer of unfulfilled expectations and distrust of institutional structures. The problems in mental health for migrants in Britain are mirrored in the education and criminal justice systems (Modood *et al*, 1997). This suggests a developmental trajectory that is affected by social and generational realities and at the same time increases the risk of presentation with psychotic symptoms.

This would mean that the risk exposure for psychosis lies not specifically in the urban environment but in the way this environment generates and/or facilitates a life course that ultimately disadvantages those whose vulnerability is not compensated for by the support of their social environment. This is also influenced by the individual's perception of the negative experiences of the ethnic and socio-cultural groups with which they identify in both the narrow family and community sense as well as the wider national and international sense.

There might therefore be a need to reconstruct the neurodevelopmental model which has led to a preoccupation with the biology of psychosis to include a social developmental model that can demonstrate how the neurobiological endpoint of psychosis can have both biological and social origins.

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Van Os (2004) discusses the implication from the epidemiological research by Sundquist *et al* (2004) that psychosis may indeed be due to urban toxicity. The dose–response increase in urbanicity with schizophrenia does incline to an explanation of causation rather than association. The discussion of a set of environmental factors acting between birth and the onset of psychosis (child and adolescence) should have led to a discussion of the role that cannabis plays in the early onset of psychosis. This link between substance use and urbanicity was, however, not discussed in the editorial.

The clue to an ecological exposure lies in the early use of cannabis. Arseneault *et al* (2002) in a prospective study found an association between early use of cannabis (by the age of 15) and an increased risk of psychosis for 1037 children born in New Zealand. This aetiological factor interacts with the increased social fragmentation, social inequality and social isolation found with greater urbanicity. The cognitive vulnerabilities for psychosis have a strong social environmental aetiology, and a link needs to be made between models of urban toxicity and increased early cannabis use.

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Memantine as a neuroprotective treatment in schizophrenia

Phospholipid metabolism occurs in cell (including neuron) membranes and although regional differences are described by Jensen *et al* (2004), these are not neurotransmitter-specific. This research suggests increased phospholipid metabolism in the anterior cingulate area of people with schizophrenia.

Jensen *et al* suggest that this is supportive evidence for a neurodegenerative mechanism in schizophrenia. They also review the effects of neuroleptic and anxiolytic (including benzodiazepine) medications on brain phosphorus metabolism.

Memantine is a drug currently licensed for use in people with moderate to severe Alzheimer's dementia. It is a non-competitive, low-affinity *N*-methyl-D-aspartate (NMDA) antagonist. (The NMDA receptor is a class of glutamate receptor.) Glutamate-mediated excitotoxicity and/or receptor dysfunction is involved in the pathogenesis of several neuropsychiatric and neurological disorders. Memantine partially blocks these NMDA receptors, preventing a neurotoxic influx of calcium. Theoretically, it is neuroprotective for glutamate-receiving neurons.

Given its mode of action, it should theoretically be more effective in the early stages of neurodegenerative disorders such as Alzheimer's dementia. On these theoretical grounds it may also be neuroprotective for people with schizophrenia.

Jensen, J. E., Miller, J., Williamson, P. C., *et al* (2004) Focal changes in brain energy and phospholipid metabolism in first-episode schizophrenia: ^{31}P-MRS chemical shift imaging study at 4 Tesla. *British Journal of Psychiatry*, **184**, 409–415.

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Authors' reply: Memantine, as described by Dr Rands, would appear to be a suitable candidate as a neuroprotective agent for people with schizophrenia, based on its NMDA-receptor-blocking properties. This drug is currently in use as a treatment for people with moderate to severe Alzheimer's dementia.

As shown by Theberge *et al* (2002, 2003), glutamate levels in first-episode schizophrenia are higher than normal in the anterior cingulate and lower than normal in this same region in the chronic stages of illness. As shown in this same work, *N*-acetylaspartate levels correlate negatively

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with duration of positive symptoms. This work, as well as the phosphorus work by our team (Jensen *et al*, 2000, 2002), suggests a gradual neurodegenerative process in the anterior cingulate in schizophrenia, possibly initiated by an early neurodevelopmental anomaly involving basal ganglia–thalamocortical neuronal circuits or the structures which regulate these circuits. As Dr Rands points out, memantine would partially block the NMDA receptors preventing excitotoxic damage in the anterior cingulate and connected structures, thus slowing the progression of symptoms. However, there are other considerations. There is evidence that excitotoxicity is linked to non-NMDA receptors (Tsai & Coyle, 2002) which may not be affected by this approach. Furthermore, another NMDA-blocker, phencyclidine, can actually cause a paradoxical increase in glutamate activity which could aggravate the condition.

In summary, we agree that treatment options for schizophrenia should begin to focus more on this neuroprotective strategy. Although current medications may alleviate positive symptoms, they are relatively ineffective for negative symptoms and are often inadequate in preventing the psychosocial deterioration seen in chronic schizophrenia. Treatment with memantine could theoretically slow the progression of negative symptoms when administered to patients in the early stages of schizophrenia but the overall effects of these drugs are difficult to predict and it is our view that some caution is indicated in planning long-term trials of these medications in people with schizophrenia.

Jensen, J. E., Miller, J., Williamson, P. C., *et al* (2000) Focal changes in brain energy and phospholipid metabolism in first-episode schizophrenia: ^{31}P-MRS chemical shift imaging study at 4 Tesla. *British Journal of Psychiatry*, **184**, 409–415.

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Testing for diabetes

Taylor *et al* (2004) report on the differences in testing for diabetes among 606 patients receiving antipsychotics, observing that patients receiving atypical antipsychotics were more likely to have been tested than those receiving older agents. Moreover, this appeared to be significant specifically for clozapine, olanzapine, and antipsychotic polypharmacy.

It is noteworthy that very similar results were found by our group when examining hospitalised patients in New York State (Citrome *et al*, 2003, 2004). Among 1154 patients in 2000–2002 with no known prior history of receiving antidiabetic medications, those receiving clozapine, olanzapine, or more than one atypical antipsychotic had a significantly higher frequency of blood glucose testing than those receiving only typical antipsychotics (Citrome *et al*, 2004). Moreover, those receiving risperidone had a frequency of testing similar to those receiving only older agents, resulting in the conclusion that there are clear differences in surveillance for diabetes mellitus among even the newer agents.

Investigators performing pharmacoepidemiological studies examining the risk of association between antipsychotics and diabetes mellitus need to be mindful of this surveillance bias.

Declaration of interest

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Taylor *et al* (2004) found very low rates of monitoring for diabetes in their study population. Less than 50% were tested, and the testing rates varied with the antipsychotic prescribed.

So why is this the case? This probably reflects the lack of a clear consensus in this area. There is currently no consistent direction for doctors regarding the need for monitoring for diabetes. The conflicting evidence in the literature is abundant. For example, the *British National Formulary* is probably the most widely used reference for prescribers in the UK. The current edition makes no mention of blood sugar abnormalities with typical antipsychotics, quetiapine and risperidone. Concerns are mainly highlighted with olanzapine and clozapine. This is despite studies showing increased risks with typical and atypical antipsychotics. Furthermore, the recent Maudsley Guidelines give some suggestions of the type and frequency of tests, focus mainly on olanzapine and clozapine but contradict the *British National Formulary* in suggesting testing for all antipsychotics.

So is testing important? Evidence is mounting of an association between schizophrenia and diabetes. Ryan & Thakore (2002) give schizophrenia as an independent risk factor for diabetes even in antipsychotic-naïve patients. The PORT study (Dixon *et al*, 2000) gives a prevalence of 15% in this population compared with 3% in the general population (Bennett *et al*, 1995). Several studies suggest an even higher risk of diabetes in those prescribed atypical antipsychotics (Bushe & Leonard, 2004). Therefore, it appears that people with schizophrenia are a high-risk group for developing diabetes and its potential consequences.

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