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CAN METABOLIC SIDE EFFECTS OF ANTIPSYCHOTICS BE REVERSED BY LIFESTYLE CHANGES?

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SUMMARY

Introduction: *Antipsychotics, particularly atypical antipsychotics, are known to have metabolic side effects such as; weight gain, hyperlipidaemia and insulin resistance. This is problematic as metabolic syndrome can be a precursor to many diseases, including type II diabetes and coronary heart disease. In an attempt to overcome these side-effects, lifestyle changes have been recommended in tandem with commencement of atypical antipsychotics, but is this effective at halting metabolic syndrome?*

Results: *There is some evidence suggesting that lifestyle changes can reduce weight gain caused by atypical antipsychotics. However, there seems to be a paucity of evidence about whether this correlates with correction of metabolic dysregulation. Moreover, there is a lack of research into the precise mechanism of metabolic syndrome as caused by atypical antipsychotics,as well as a lack of evidence into how exercise remedies this. Furthermore, there is research to suggest that the pathophysiology of psychosis may lead to metabolic dysregulation independently of treatment.*

Conclusion: *Lifestyle changes should still be part of a treatment as they seem to partially reverse metabolic changes seen with atypical antipsychotics. However, more research is needed to identify weight independent mechanisms for metabolic dysregulation seen in those taking atypical antipsychotics in order to solve this pressing issue.*

Key words: *antipsychotic drugs – atypical - lifestyle changes - metabolic syndrome - weight gain*

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INTRODUCTION

Antipsychotic medication is the cornerstone of treatment of psychosis, and the introduction of atypical antipsychotics into the pharmacological arsenal has been invaluable in the improvement of outcomes for those with psychosis. These newer drugs have a different side effect profile to the first generation antipsychotics - showing fewer of the neurological effects, but exhibiting marked metabolic dysregulation. Clinical trials have shown that atypical antipsychotics can cause weight gain, increased central adiposity, hyperlipidaemia and insulin resistance (Meyer 2008, Patel 2009, Saddichha 2007, Shin 2012, Smith 2007, Smith 2009, Kozumplik 2010, Babić 2010). This has wide reaching public health ramifications - the most pressing of which are an increase in the diabetes prevalence (Manu 2012) and cardiovascular disorders (Leung 2012) in this group. This decreases medication compliance and further stigmatises these vulnerable patients (Lieberman 2005).

Treatment to counteract these metabolic side effects, as recommended by NICE, is advice on lifestyle changes (NICE 2014). This includes advice on healthy eating and exercise regimes (Bushe 2005). Once these patient reach diabetic threshold they are then put onto the NICE diabetic pathway (NICE, 2012). The question to be highlighted in this article is "What evidence is there to suggest that lifestyle changes can reverse the metabolic side effect profile brought about by atypical antipsychotic medication?"

DISCUSSION

According to NICE guidelines CG178 "Psychosis and schizophrenia in adults: treatment and management" recommendation 1.1.3.1 "people with psychosis or schizophrenia, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity plan by their mental healthcare provider". It goes on to explain in further detail that metabolic dysregulation can be measured within weeks of starting atypical antipsychotics.

NICE uses evidence from 28 randomised control trials that fit into their criteria to evaluate whether physical activity and healthy eating interventions are effective in the control of weight in those with psychosis on treatment. Although the evidence was deemed to be low quality, there seemed to be some concordance between the studies that these lifestyle interventions had a significant effect on reducing weight (or weight gain) compared to those in non-intervention groups (Álvarez-Jiménez 2006, Álvarez-Jiménez 2008, Álvarez-Jiménez 2010, Attux 2011, Ball 2001, Bushe 2008, Casagrande 2010, Cordier 2013, Das 2012, Daumit 2011, Evans 2005, Goldberg 2013, Hester 2005, Hoffmann 2005,

Holt 2010, Kalarchian 2005, Littrell 2003, McElroy 2009, Milano 2007, Niv 2012, Pendlebury 2005, Pendlebury 2007, Porsdal 2010, Poole Hoffmann 2008, Ratcliff 2012, Scocco 2006, Skouroliakou 2009, Smith 2007, Smith 2007,Vreeland 2003, Cabassa 2010). This can be seen all the way through to recent trials (Attux 2013, Daumit 2013, Usher 2012), where the first two of these papers suggest that the intervention causes statistically significant weight change, whereas the last one reports no statistical significance. The same conclusion was not found in those trials which only promoted physical activity, as opposed to a more holistic physical activity and healthy eating regime. Some studies have in fact measured some metabolic factors, such as lipid levels, glucose levels, and HbA1c levels before and after dieting (Beaulieu 2003, Bonfioli 2012, Caemmerer 2012, Centorrino 2006, Chen 2009, Cordes 2011, Gabriele 2009, Kuo 2012, Lindenmayer 2009, Kwon 2006, Mauri 2008, Menza 2004, Poulin 2007, Hassapidou 2011).

A recent review by Caemmerer et al. (2012) found out that intervention patients experienced significant decreases in waist circumference, percent body fat, glucose, insulin, total cholesterol, low density-lipoprotein-cholesterol and triglycerides compared to controls. Poulin et al. (2007) also found that there was an improvement in high-density lipoprotein-cholesterol (HDL), which were and significantly increased , and LDL cholesterol, triglycerides and total cholesterol were decreased, in their study group compared with controls. Similar results were found by Hassapidou et al. (2011).

Focusing on the specific metabolic parameters, Centorrino et al. (2006) obtained an 11% improvement of blood pressure levels (from 130/83 mmHg to 116/74 mmHg) after a weight reduction program as did Kwon et al. (2006).

As for glucose metabolism, Mauri et al. (2008) reported an improvement in hepatic insulin sensitivity while Cordes et al. (2011) discovered that the intervention patients showed a significantly smaller increase in fasting glucose and 2-h glucose after oral glucose load than controls. Poulin et al. (2007) also found that there was an improvement in fasting blood glucose in their study group. Caemmerer et al. (2012) and Hassapidou et al. (2011) had similar results for blood glucose.

Furthermore, Gabriele et al. (2009) stated that the behavioural weight loss interventions were found to improve insulin regulation and HbA1c. Poulin et al. (2007) also found that there was an improvement in Hba1c in their study group.

Lindenmayer et al. (2009) showed that the percentage of patients who met criteria for metabolic syndrome decreased from 25.46% at baseline to 19.56% at endpoint. In addition, a statistically significant reduction in triglyceride level was found in this research while furthermore Kwon et al. (2006) reported a change from baseline of the ratio of low-density and high-density lipoproteins.

Poulin et al. (2007) also found no significant changes were observed regarding serum concentrations of prolactin and TSH during the study.

Worthy to note, an interesting research (Kuo 2012) reported that serum BDNF levels were positively correlated with body weight and body mass index reduction. These results are encouraging in showing that exercise and dietary changes improve aspects of metabolic disregulation in patients on antipsychotics , but it is clear that all these papers measure different aspects of metabolic disregulation . Therefore it is necessary that further studies be made to demonstrate that all parameters are affected positively by dietary changes and exercise and that the improvement can be maintained in the long term.

Lifestyle recommendations have been made mainly to include dietary changes rather than increase of physical activity alone,indeed, one of the well know side effects of atypical antipsychotics is an increase in appetite (Blouin 2008). Although it is conceeded that this is mainly due to a paucity of evidence –the assumption that appears to have been made is that by preventing weight gain we are preventing metabolic dysregulation.This seems to be based on the evidence of a review (Newcomer 2006) that relative risk for Type II Diabetes with different antipsychotics is matched with potential for that antipsychotic to cause weight gain. This same review however pointed out that a significant minority of patients suffered metabolic dysregulation without weight gain. This suggests that although the metabolic syndrome has a weight dependent mechanism, there is also a weight independent mechanism induced by the atypical antipsychotics. This has been further explored by other articles. Teff et al. (2013) demonstrated that olanzpine can rapidly induce metabolic dysregulation without weight gain, by causing postprandial hyperinsulinaemia and increased incretin release in response to meal ingestion. This led them to postulate that metabolic dysregulation can occur due to compensatory overaction of vagal efferents, due to olanzapine antagonising peripheral muscarinic receptors. Although it is difficult to draw such large conclusions from a paucity of evidence, what has been suggested by Irwin and Gault (2013) is that if there is a weight independent mechanism for metabolic dysregulation, then measures put in place to prevent metabolic disease in those taking antipsychotics will only be partially effective.

To the best of our knowledge, there has only been one experiment, Boyda et al. (2014), which has aimed to show the effects of exercise on metabolic dysregulation in the absence of weight change. This experiment was done in olanzapine treated rodents. This was felt to be analogous to humans as they exhibit a similar side effect profile in response to olanzapine (Albaugh 2011). Their results show decreased glucose tolerance in those rats treated with olanzapine, however, this was partially compensated by routine exercise by the 4th week of the regime. This was hypothesised to be due to upregulation

of GLUT4 receptor in exercise. This has also been hypothesised as a mechanism in Type II Diabetes (Wang 2009) where there is a more substantial body of evidence. Although this data is promising, particularly as an interesting foray into an under-researched area, there are some reservations in application. First of all, its small sample size and short time course (n=8-10 per group, length of time =8 weeks). This makes it very difficult to make meaningful conclusions. Furthermore, weight gain in rat models treated with olanzapine does not mirror human experiences. The rats show weight gain in the first few weeks (Albaugh 2006) however this pattern is not necessarily continued, as seen in longer studies (Chintoh 2008). Indeed in this experiment, the evidence showed no increased weight gain for the olanzpine treated rats despite increased calorie intake. Since metabolic dysregulation in humans seems to be partially caused by weight-related mechanisms, we must question how accurate these rat models are.

It should be pointed out that according to NICE's cost per QALY projections based upon Winterbourne et al. (2013) the cost effectiveness of advice on lifestyle changes would be £960 per QALY. This is deemed very cost effective, as it is substantially below NICE's lower cost effectiveness threshold of £20,000. This is probably a contributing factor to NICE's advocation of lifestyle changes in those taking antipsychotics, despite the low evidence base on which to champion them.

Part of the reason for the belief that atypical antipsychotics could cause metabolic syndrome is based in the observation that patients taking atypicals have higher rates of metabolic dysregulation than those taking their typical counterparts (Newcomer 2007). Furthermore, it can be seen that certain atypical antipsychotics can exert a greater effect than others, with clozapine and olanzapine being the most potent (Torrent 2008). This however may oversimplify the heterogeneity seen in people with psychosis. Research has suggested that schizophrenia itself may be an independent risk factor for impaired glucose tolerance and Type II Diabetes (Bushe 2004, Reddy 2013). This could be to some extent because of hormonal changes seen in those with mental illness.Goh and Agius (2010) demonstrated that stress responses are altered in those with mental illness via hypercortisolaemia. Hypercortisolaemia is also seen in metabolic syndrome (Musselman 1998) suggesting hormonal dysregulation which occurs as part of the pathophysiology can be implicated in metabolic syndrome.

Additionally, different disease profiles may show different responses to lifestyle changes. Ventriglio et al. (2014) demonstrated that although improvements could be seen in both the bipolar and the schizophrenic groups, the bipolar group showed a greater improvement. This would lead us to suggest that disease factors also contribute to weight gain and metabolic dysregulation as part of an independent mechanism from the antipsychotics. More research is needed if we are to find a solution to counteract these effects.

CONCLUSION

Metabolic syndrome and its consequences have drastic effects of mortality and quality of life on those affected by it. People with psychosis are particularly vulnerable to suffering from metabolic dysregulation and therefore treatment to counteract this is paramount. There is evidence to suggest that lifestyle changes can partially reverse the weight gain associated with atypical antipsychotics and therefore can partially reverse the metabolic syndrome seen in this group. However,this simple solution does not entirely solve what is a more complex problem. It seems that atypical antipsychotics can cause a weight independent mechanism for glucose intolerance. In addition, psychiatric disorders themselves seem to intrinsically have a role in contributing to metabolic dysregulation, independent from the treatment. It has been commented in many papers, including in the NICE guidelines, that there is a paucity of evidence in this field. Thus it is difficult to draw meaningful conclusion of both mechanism and treatment of metabolic syndrome in those taking antipsychotics.

To conclude, lifestyle changes seem to have a partial effect on reversal of metabolic side effects of antipsychotics, and thus should be continued to be promoted as a treatment.

Furthermore, it is necessary that, apart from improvement to diet and exercise, patients on antipsychotics should be monitored regularly for markers of metabolic disregulation, including lipid levels, HbA1c, and Glucose levels, as well as hypertention, weight, BMI, and abdominal girth. This is recommended by NICE (2014), the influential Maudsley Guidelines (Taylor 2009) and also by the European Psychiatric Association (De Hert 2009, De Hert 2011). It would be very useful if many further studies are carried out which measure these factors, in order to confirm that reports of the above metabolic improvements are effective in the long term, given the possibility that the metabolic disregulation is not only caused by the antipsychotics, but also by the nature of the illness of schizophrenia itself (Bushe 2004, Reddy 2013).

Further caution needs to be exercised when attempting to apply the data we have reviewed to a system such as the British one, when it is expected that primary care should take over the monitoring of Metabolic Disregulation for mental health patients in the long term. A recent systematic review (Nover 2013) reported that no studies were available to measure the effectiveness of this approach to monitoring metabolic disregulation related to long term antipsychotic medication in the long term in primary care.Clearly it is necessary that this approach needs to be studied and reported on. Furthermore, it is of the essence that a shared care protocol, and a method for primary and secondary care to share information-such as a shared care card system similar to the UK Lithium card, on which both primary and secondary physians can write

and which is held by the patient- is necessary in order for such a system of monitoring to be instituted effectively.

However, further research needs to be done in these areas to fully understand and integrate the factors involved in metabolic dysregulation in those taking antipsychotics. By achieving this, we should be able to find a better solution to the problem of metabolic dysregulation caused by antipsychotics.

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