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Changes in biomarkers of bone turnover in an aripiprazole add-on or switching study

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ABSTRACT

Background: The association between mental illness and osteoporosis and fractures is particularly pronounced in psychotic disorders. Antipsychotic use has previously been described to affect bone density.
Method: A 52-week follow-up of patients switched to aripiprazole or with aripiprazole added on, conducting a specific analysis of markers of bone turnover: urinary NTX (a biomarker of bone resorption) and serum BSAP (a biomarker of bone formation). Baseline and serial measurements of bone markers NTX, BSAP and of hormones prolactin, oestrogen and testosterone were done at weeks 0 and 1, 2, 6, 12, 26 and 52, respectively.
Results: NTX concentration reduced over time but this did not reach significance in the whole group (log-NTX: $\beta = -0.0012$, $p = 0.142$). For BSAP the addition of or replacement with aripiprazole produced a significant reduction (log-BSAP: $\beta = -0.00039$, $p = 0.002$). Analysis with prolactin similarly showed a significant reduction (log-prolactin: $\beta = -0.0024$, $p < 0.001$); other hormones did not change significantly. Sensitivity analysis to compare the switchers to aripiprazole versus the "add-on" showed that the former group had a significant reduction in NTX.
Conclusions: We found that switching to aripiprazole was associated with changes in molecular biomarkers of bone resorption, indicating a more favourable profile for bone health.

1. Introduction

Severe mental illness is associated with an increased risk of comorbid physical illness (De Hert et al., 2011). The basic aetiology of these associated conditions is often three-fold: less than ideal lifestyle management, physiological or endocrine dysfunction related to the pathology underlying the specific mental illness, and physiological disruption induced by psychotropic medication.

Osteoporosis is one of the physical illnesses associated with severe mental illness, with schizophrenia being associated with particularly high rates of this condition and reduced bone density in both women and men (Hummer et al., 2005; Leucht et al., 2007; Bolton et al., 2011; Kishimoto et al., 2012; Kinon et al., 2013; Wu et al., 2013). A meta-analysis found that rates of osteoporosis were two and half times more in patients with schizophrenia than controls, while rates of reduced bone density were twice as much (Stubbs et al., 2014). Incidence of fractures can be used as an indirect indicator of the reduced bone mineral density (BMD) that defines osteoporosis. In a large cohort of patients, Abel et al. (2008) observed a significant increase in relative fracture risk associated with psychotic disorders (RR 5.12 and 6.41 for females and males aged 45–74 years, respectively) that was not observed for the combined psychiatric disorder cohort (RR 1.90 and 1.4, respectively) (Abel et al., 2008). Stubbs et al. (2015) in a recently published meta-analysis confirmed higher occurrence of fractures in patients with schizophrenia compared to controls (Stubbs et al., 2015).

One major contributing factor to the accelerated trajectory towards osteoporosis observed in schizophrenia may be the use of prolactin-raising antipsychotics, which are independently associated with the incidence of hip fractures (Howard et al., 2007), and higher rates

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of bone pathology (O'Keane and Meaney, 2005). Drug-induced hyperprolactinemia and associated dysfunction of the hypothalamo-pituitary-gonadal axis results in diminished concentrations of oestrogen and testosterone (Halbreich et al., 2003; Meaney et al., 2004; Misra et al., 2004; Hummer et al., 2005; Wyszogrodzka-Kucharska and Rabe-Jablonska, 2006). This can accelerate BMD decline. In this regard, O'Keane and Meaney (2005) observed that elevated prolactin concentrations were related to hypogonadism and low BMD (O'Keane and Meaney, 2005) in young women with schizophrenia.

We have previously described a 26-week, open-label, intention-to-treat study of patients with schizophrenia who either switched from or had aripiprazole added on to their treatment in which we observed that switching/adding-on aripiprazole resulted in significantly reduced prolactin concentrations at 12 weeks ($p = 0.003$) and the decreased concentrations persisted to the end of the 26-week study period ($p < 0.001$) (Mir et al., 2008). In the data presented here, we report on the 52-week follow-up of the same patients switched to aripiprazole or with aripiprazole added on, conducting a specific analysis of markers of bone turnover. Our aim was to determine if the addition of and/or switch to aripiprazole resulted in maintenance of the reduction in prolactin concentration to the 52-week time point, favourably affected the biomarkers of bone resorption/formation, and effected any changes in oestrogen and testosterone concentration. In this study, urinary type I collagen cross-linked N-telopeptide (NTX), a marker of bone resorption, and serum bone-specific alkaline phosphatase (BSAP), a marker of bone formation (Singer and Eyre, 2008; Wheater et al., 2013) were used. NTX and BSAP concentration reflect the degree of bone turnover at the whole body level.

To our knowledge, this is the first report of a prospective or longitudinal analysis of these biomarkers in patients with schizophrenia who had a change in antipsychotic treatment regime. We hypothesised that the change to medication profile would be associated with a reduction in prolactin and urinary NTX, and that there would be a change in BSAP.

2. Methods

Individuals were recruited and followed up as described in Mir et al. (2008) and Aitchison et al. (2011) from the COAST Team (Croydon Early Intervention in Psychosis Service), the Croydon Rehabilitation Team, and Croydon Community Mental Health Teams. In brief, the inclusion criteria were subjects (male or female) in the age range 18 to 65 years, who had a psychotic illness and lived in the community (outpatients), and failed to respond adequately to another antipsychotic (either inadequate therapeutic response or intolerance). There were no restrictions in terms of other factors such as ethnicity. The exclusion criteria were pregnancy and breast-feeding.

An open-label add-on or switch to aripiprazole was offered to eligible participants. The starting dose at the commencement of the study was 10 mg for all subjects, but was reduced to 5 mg once the 5 mg tablets became available in the UK (January 2005). Details of the flexible dose titration schedule, cross taper or concomitant administration of other antipsychotic with aripiprazole and study group are detailed by Mir et al. (2008) and Aitchison et al. (2011).

Thirty-six subjects were referred and deemed eligible for participation. Of these, eight subjects refused participation and of the 28 included, one withdrew prior to the commencement of medication because of non-compliance with any of the medications that were offered. Therefore, 27 were included; however, analysable bone marker or hormone data were available for 26 patients. Eighteen subjects reached the endpoint of the study at 52 weeks, while nine dropped out prior to 52 weeks (Aitchison et al., 2011). Four patients dropped out due to lack of improvement (at weeks 8, 18, 27 and 27), four patients dropped out due to non-adherence (at weeks 2, 5, 35 and 48) and one dropped out due to deportation from the country. Patients who were non-adherent were refusing to take any pharmacological treatment at the time of dropout and had a history of non-adherence.

2.1. Laboratory analyses

Serial measurements of prolactin, testosterone, and 17-β oestradiol were performed and reported to 26 weeks in the initial study by Mir et al. (2008), using the methods on the ADVIA Centaur immunoassay analyser (Siemens Diagnostics, Frimley, Surrey, UK) (Mir et al., 2008). Serum concentrations of BSAP, albumin, cholesterol, calcium (for which a corrected value was produced), urinary creatinine, and urinary NTX were also measured. The time points for all biological markers were: baseline (0 weeks), 1, 2, 6, 12, 26, and 52 weeks. In addition, for some patients who had been unable to attend the predetermined follow up time points, concentrations of biological markers were present at weeks 18, 22, 30 and 35. The blood draws and urine collection were done between approximately 12 p.m. and 3 p.m., providing relative consistency in timing of sample collection. All available data on the biological markers were used in the analysis.

NTX was measured in the samples using the osteomark assay, which is a competitive-inhibition enzyme-linked immunosorbent assay (ELISA). NTX concentration was quantified spectophotometrically and calculated using a standard calibration curve. A urinary creatinine analysis of the NTX assay values was then used to correct for urinary dilution, producing values labelled 'NTX', expressed in nanomoles of bone collagen equivalents (nmol BCE) per millimole creatinine (mmol creatinine). BSAP was measured in the serum samples using an enzyme-linked immunosorbent assay (ELISA, Ostase, IDS, Boldon, UK).

Table 1
Demographic and clinical characteristics of patients where sufficient data was available and those not included or dropped out prior within two weeks of the study, from 28 patients, over 52 weeks of the study.

	Included	'Drop-outs'
	N = 26 (92.1%)	N = 2(7.9%)
Sex		
Male, N (%)	13 (50)	1 (50)
Female, N (%)	13 (50)	1 (50)
Mean Age, years (SE)	27.53 (7.7)	23 (2.08)
Age range, years	18–45	18–45
Ethnicity		
White, N (%)	13 (57.7)	2 (100)
Black, N (%)	6 (15.4)	0 (0)
Asian, N (%)	3 (19.2)	0 (0)
Mixed, N (%)	1 (4.3)	0 (0)
Diagnosis		
Schizophrenia, N (%)	15 (57.7)	1 (50)
Schizoaffective, N (%)	6 (15.4)	0 (0)
Bipolar Affective Disorder, N (%)	1 (3.8)	0 (0)
Psychotic Depression, N (%)	6 (23)	1 (50)
Years of psychotic illness		
<1 year, N (%)	0	0 (0)
1–3 years, N (%)	7 (26.9)	0 (0)
3–5 years, N (%)	7 (26.9)	1 (50)
5–7 years, N (%)	5 (19.3)	1 (50)
7–9 years, N (%)	2 (7.7)	0 (0)
9–11 years, N (%)	2 (7.7)	0 (0)
>11 years, N (%)	3 (11.5)	0 (0)
Antipsychotic prior to switching (baseline medication)		
Amisulpride, N (%)	3 (10.7)	1 (50)
Risperidone, N (%)	8 (28.5)	1 (50)
Quetiapine, N (%)	3 (10.7)	0 (0)
Olanzapine, N (%)	10 (35.7)	0 (0)
Clozapine, N (%)	1 (3.5)	0 (0)
Zuclopenthixol, N (%)	1 (3.5)	0 (0)