Anticholinergic burden in schizophrenia and ability to benefit from psychosocial treatment programmes: a 3-year prospective cohort study

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Background. Many medications administered to patients with schizophrenia possess anticholinergic properties. When aggregated, pharmacological treatments may result in a considerable anticholinergic burden. The extent to which anticholinergic burden has a deleterious effect on cognition and impairs ability to participate in and benefit from psychosocial treatments is unknown.

Method. Seventy patients were followed for approximately 3 years. The MATRICS consensus cognitive battery (MCCB) was administered at baseline. Anticholinergic burden was measured with the Anticholinergic Cognitive Burden (ACB) scale. Ability to benefit from psychosocial programmes was measured using the DUNDRUM-3 Programme Completion Scale (D-3) at baseline and follow-up. Psychiatric symptoms were measured using the PANSS. Total antipsychotic dose was measured using chlorpromazine equivalents. Functioning was measured using the Social and Occupational Functioning Assessment Scale (SOFAS).

Results. Mediation analysis found that the influence of anticholinergic burden on ability to participate and benefit from psychosocial programmes was completely mediated by the MCCB. For every 1-unit increase on the ACB scale, change scores for DUNDRUM-3 decreased by −0.27 points. This relationship appears specific to anticholinergic burden and not total antipsychotic dose. Moreover, mediation appears to be specific to cognition and not psychopathology. Baseline functioning also acted as mediator but only when MCCB was not controlled for.

Conclusions. Anticholinergic burden has a significant impact on patients’ ability to participate in and benefit from psychosocial treatment programmes. Physicians need to be mindful of the cumulative effect that medications can have on patient cognition, functional capacity and ability to benefit from psychosocial treatments.

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Key words: Anticholinergic burden, cognition, MCCB, psychosocial treatments, schizophrenia.

Introduction
The neurocognitive theory of schizophrenia has demonstrated explanatory reach (Deutsch, 2011; Kahn & Keefe 2013). Cognitive impairment accounts for a range of outcomes including ability to live independently, employment, quality of life and reactive violence in addition to response to antipsychotic medication (Kim et al. 2008; Chang et al. 2013; Kahn & Keefe, 2013; O’Reilly et al. 2015). Although pharmacotherapy is the primary treatment for the symptoms of schizophrenia (Leucht et al. 2012) such as delusions and hallucinations, it is less effective for negative symptoms like lack of motivation, nor is it effective for cognitive impairment (Harvey & Bowie, 2012; Nielsen et al. 2015). Only one in seven patients achieve recovery when defined as clinical and social adaptation sustained over time (Jääskeläinen et al. 2013). Psychosocial treatments are generally used to address the functional disability that characterizes schizophrenia (Grant et al. 2011). Unfortunately cognitive problems may also interfere with the effectiveness of these interventions (Green et al. 2000; Kurtz, 2011; O’Reilly et al. 2016).

To facilitate the development of cognitive enhancing agents the US National Institute of Mental Health devised a neuropsychological battery for treatment studies, the MATRICS consensus cognitive battery (MCCB; Nuechterlein et al. 2008). The US Food and Drug Administration (FDA) requires that cognitive enhancing agents be supported by both evidence of
change in cognitive performance and improvements in ‘real world’ functioning (Buchanan et al. 2005). Currently pharmacological attempts to enhance cognition among patients with schizophrenia have been unsuccessful (Harvey & Bowie, 2012). The reason for this is unclear. Excessive synaptic pruning may limit the potential for improving cognition via neurotransmitters (Keshavan et al. 1994; Harvey & Bowie, 2012; Sekar et al. 2016). But the use and dose of concurrent medications may also be important (Harvey & Bowie, 2012). One mechanism through which a deleterious effect of concurrent medications might occur is via the cholinergic system (Nebes et al. 2005; Campbell et al. 2009). The cholinergic system is a series of pathways from the basal forebrain radiating throughout the cerebral cortex and involved in regulating attention and memory (Chudasama et al. 2004; Sarter et al. 2005).

Most antipsychotic medications administered to patients with schizophrenia possess anticholinergic properties (Chew et al. 2008). The side-effect profile of antipsychotic medication is also sometimes treated with anticholinergic agents. In recognition of this the FDA-NIMH-MATRICS Guidelines for Clinical Trial Design of Cognitive-Enhancing Drugs require that first-generation antipsychotics can be utilized in clinical trials but only with no additional anticholinergic agents (Buchanan et al. 2011). Over 50% of people with schizophrenia also have other psychiatric or general medical conditions which require treatment (Green et al. 2003; Jones et al. 2004). Many medications for treating these non-psychiatric problems have anticholinergic properties. Pharmacological treatments when aggregated may create a considerable anticholinergic burden that impairs cognition, functional capacity and ability to benefit from psychosocial treatments amongst a group of patients who are already cognitively impaired (Vinogradov et al. 2009; O’Reilly et al. 2015).

To our knowledge only one study has investigated whether anticholinergic burden moderates the effectiveness of behavioural treatments (Vinogradov et al. 2009). Serum anticholinergic activity uniquely accounted for 20% of the variance in change of global cognition following a programme of cognitive remediation therapy, independent of age, IQ or symptom severity. A limitation of this study was that it consisted of patients who were treatment responsive and who volunteered to participate in 50 hours of intensive therapy. Moreover, the study was limited to cognitive outcome and did not examine the effect of anticholinergic burden on functional status. Because cognitive impairment in schizophrenia is an important goal of treatment and because cognitive deficits are known to affect patients’ ability to benefit from psychosocial programmes it is necessary to examine whether anticholinergic burden affects patients’ ability to benefit from treatments.

(1) We hypothesized that the relationship between anticholinergic burden and ability to benefit from psychosocial treatment programmes would be mediated by cognitive ability, when controlling for age, gender, baseline performance on psychosocial treatment programmes, total antipsychotic dose, and symptoms.

(2) We hypothesized that the mediation relationship between medication, cognition, and programme completion would be specific to anticholinergic burden and not total antipsychotic dose; and that the mediation would be specific to cognition, not to symptoms or functioning when cognition is controlled for.

Method

This was a naturalistic 3 year prospective observational cohort study of anticholinergic burden, cognitive ability and patient benefit from psychosocial treatment programmes. Data were gathered from 2012 to 2015. Baseline data was gathered in 2012. Follow up data was gathered until the end of 2015. All of the assessments were completed by assessors who were blind to the results of the other assessments.

Participants and setting

The National Forensic Mental Health Service (NFMHS) for Ireland provides specialized care for adults who have a mental disorder and are at risk of harming themselves or others. At the time of the study the NFMHS had 94 secure inpatient beds located on a single campus, the Central Mental Hospital (CMH), and 13 supervised community beds for those discharged subject to conditions. The CMH is the only secure forensic psychiatric hospital for the Republic of Ireland.

Inclusion criteria were having a diagnosis of schizophrenia or schizoaffective disorder and being judged to be able to provide informed consent. A total of 123 patients were invited to participate during 2012. Of these eight patients declined to take part and 15 did not have a diagnosis of schizophrenia or schizoaffective disorder as assessed by a consultant psychiatrist using the Structured Clinical Interview for DSM-IV (SCID; First et al. 2002). Of the 100 remaining, 19 patients were discharged and one patient died before they could complete the programme completion assessment at follow-up, one patient was judged to be feigning during the assessment, and one patient did not complete the cognitive assessment, while eight patients did not complete the Positive and
Negative Syndrome Scale (PANSS; Kay et al. 1987) assessment. Of the 70 patients that remained in the study, 59 patients have a SCID diagnosis of schizophrenia and 11 a diagnosis of schizoaffective disorder. There were 66 male (94.3%) and four female (5.7%) patients. The mean age of patients in the study was 39 years (S.D.=11.1).

The mean length of stay at baseline for the 70 patients was 7.73 years (S.D.=8.07), median 5.79. Of the 70 patients included in the study, 62 (88%) remained in the study until 2015. Seven patients were discharged during the 3-year follow-up and one patient died. As assessments were carried out every 6 months, the last assessment was taken. Demographic details and sample characteristics are presented in Table 1.

### Cognitive assessment

Patients were assessed using the Measurement and Treatment to Improve Cognition in Schizophrenia (MATRICS) Consensus assessment battery of cognitive deficits in schizophrenia (MCCB), and also the Test of Premorbid Functioning (TOPF-UK; Wechsler, 2011). The mean MCCB composite score was 21.3 (S.D.=14).

Scores for estimated pre-morbid intelligence (TOPF-UK) were not adjusted for education as an estimate of premorbid ability because the symptoms associated with mental disorder can affect educational attainment. A small number of patients (n=7) could not complete the TOPF-UK because of literacy problems. The mean estimated premorbid IQ was 96.8 (S.D.=12.0).

### Functional performance

The Social and Occupational Functioning Assessment Scale (SOFAS) was completed by a member of the multidisciplinary team responsible for the care of the patient, who was blind to the other assessments including the cognitive assessment (Rybarczyk, 2011). The mean score on the SOFAS was 57 (S.D.=20).

### Programme completion

The DUNDRUM-3 Programme Completion Scale (D-3) is a structured clinical judgement instrument taken from the DUNDRUM toolkit which assesses whether patients have participated in, engaged and benefited from psychosocial programmes (Kennedy et al. 2010). An independent review found that the scale met requirements for routine outcome measures examining functioning, recovery, risk and placement pathways within forensic mental health populations (Shinkfield & Ogloff, 2014). The D-3 has also been shown to distinguish significantly between groups of patients at different levels of therapeutic security within a forensic setting (Davoren et al. 2012); and it has been shown

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### Table 1. Demographics and sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>n=70</th>
<th>Mean (range)</th>
<th>Median</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.5</td>
<td>37.5</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>66 male, 4 female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay at baseline (years)</td>
<td>7.73</td>
<td>5.79</td>
<td>8.07</td>
<td></td>
</tr>
<tr>
<td>Length of follow up period (years)</td>
<td>2.94</td>
<td>3.24</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Baseline D-3</td>
<td>16.54</td>
<td>17</td>
<td>6.63</td>
<td></td>
</tr>
<tr>
<td>Follow up D-3</td>
<td>15.01</td>
<td>13</td>
<td>7.36</td>
<td></td>
</tr>
<tr>
<td>Change score D-3</td>
<td>1.52 (range 29)</td>
<td>1</td>
<td>5.22</td>
<td></td>
</tr>
<tr>
<td>Estimate of Premorbid Intelligence TOPF-UK (standard score)</td>
<td>96.8</td>
<td>98</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>MCCB Composite (t score)</td>
<td>21.3</td>
<td>21.5</td>
<td>14.25</td>
<td></td>
</tr>
<tr>
<td>SOFAS</td>
<td>56.64</td>
<td>59</td>
<td>19.72</td>
<td></td>
</tr>
<tr>
<td>PANSS Total score</td>
<td>64.12</td>
<td>60</td>
<td>21.67</td>
<td></td>
</tr>
<tr>
<td>CPZeq (mg/day)</td>
<td>529.15</td>
<td>471</td>
<td>339.45</td>
<td></td>
</tr>
<tr>
<td>ACB score</td>
<td>4.40 (range 14)</td>
<td>3</td>
<td>2.80</td>
<td></td>
</tr>
</tbody>
</table>

D-3, DUNDRUM-3 Programme Completion Scale; TOPF, Test of Premorbid Functioning; MCCB, Matrics consensus cognitive battery; SOFAS, Social and Occupational Functioning Assessment Scale; PANSS, Positive and Negative Symptom Scale; CPZeq, chlorpromazine equivalent; ACB, Anticholinergic Cognitive Burden scale.
to predict moves between levels of therapeutic security and to predict conditional discharge from a secure hospital (Davoren et al. 2013).

The D-3 has seven items measuring outcomes for programmes concerning physical health, mental health, drugs and alcohol, problem behaviours, self-care and activities of daily living, education occupation and creativity, and family and social networks. These items are intended to cover the domains of health defined by the WHO (1986), which holds that health is ‘a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities.’ Each item is rated on a 5-point scale with lower scores representing a higher level of participation, sustained engagement and change. Engagement is demonstrated through more than simply having attended all sessions of a programme. This battery of assessments encompasses the range of interventions typically offered for patients with schizophrenia in a modern forensic hospital over a time scale of years rather than months. Annual audits during the period of this study showed that patients achieved a target of 25 h a week of timetabled therapeutic activity and represents ‘treatment as usual’.

The mean D-3 score at baseline was 16.5 (S.D.=6.63) which is the total score for all seven items. The mean D-3 at follow up was 15.0 (S.D.=7.36). D-3 change scores were calculated by subtracting the D-3 score at follow-up from the D-3 at baseline to estimate the strength of the anticholinergic effect. The mean change in D-3 score over the follow-up period was 1.52 (S.D.=5.22).

**Symptom assessment**

The PANSS was completed on all 70 patients who remained in the study. The PANSS assessments were completed by a psychiatrist registrar and an assistant psychologist trained in its use, who were blind to the cognitive assessments. The mean PANSS Total score at baseline was 64 (S.D.=22).

**Medication**

A recent review indicated that evidence is not sufficiently robust for any one of a number of methods of calculating dose equivalence for different antipsychotic medications to be considered as a gold standard, and justification should be offered for the method chosen in any particular study (Patel et al. 2013) A chlorpromazine equivalent (CPZeq) was calculated for each participant as a measure of his/her relative daily dose of antipsychotic medications (Taylor et al. 1994; Woods, 2003; Haddad et al. 2010). CPZeq was selected for calculating antipsychotic dose as it is a widely used and coherent method, appeared to have the best face validity for the purposes of this study and produces similar results to other approaches such as the British National Formula percentage maximum dose and defined daily dose (Sweileh et al. 2014). The mean CPZeq score at baseline was 529.15 mg/day (S.D. =339.45).

**Anticholinergic burden**

Anticholinergic burden was assessed using the Anticholinergic Cognitive Burden (ACB) scale (Boustani et al. 2008). The ACB scale was developed by a multidisciplinary expert panel based on a systematic review of medications with known anticholinergic activity likely to have an effect on cognition. The ACB scale contains 88 listed medications. Each listed medication can be rated on a 4-point scale (0–3): 0 = no anticholinergic activity, 1 = mild anticholinergic activity, 2 = moderate anticholinergic activity, and 3 = severe anticholinergic activity. The total anticholinergic burden is then calculated by aggregating the score for each listed medication. The ACB scale has been validated in a range of studies (Salahudeen et al. 2015).

The ACB scale was scored from prescription charts by a consultant psychiatrist (P.O’C.) the week prior to the baseline cognitive assessment. The mean ACB score at baseline was 4.40 (S.D.=2.80), mode 3; 75% of the sample had an ACB score <6. Table 2 shows that many of the medications contributing to ACB score were non-psychiatric. No benzodiazepines were prescribed.

**Statistical analysis**

Distributions of all measures were screened for outliers and evaluated for normality. One case was assessed as being an outlier on the ACB scale using an outlier labelling method and visual inspection of plots. This case was winsorized to the value of the next highest case not considered an outlier. Four cases were determined to be outliers for the change score on the D-3. These cases were also winsorized to the next highest or lowest case not considered to be an outlier. Following the removal of outliers both the ACB score and the D-3 change scores were normally distributed. The variables age, baseline 2012 D-3 and CPZeq were not normally distributed and were transformed using log10 and Srt transformation. The PANSS Total score and the MCCB Total score met criteria for a normal distribution and did not require any transformations.

A paired sample t test was used to calculate whether there was a significant difference between patients’ performance on the D-3 at baseline and 3 years follow-up. Morris & DeShon’s (2002) within-group effect-size formula was used to calculate the magnitude of the effect size over a 3-year period.
SPSS PROCESS macro model 4 (Hayes, 2013) was used to analyse mediation relationships between anticholinergic burden measured by the ACB scale and change of D-3 scores over a 3-year period in scores on the D-3. Unstandardized effect sizes were generated for the mediation models using 10,000 bootstrap samples and 95% bias-corrected confidence intervals were calculated. Age and gender were entered as covariants for all coefficients (Fig. 1).

Six specific mediation analyses were carried out to test the specificity of the relationship between anticholinergic burden, cognition, and patients’ ability to participate in and benefit from treatment programmes (change in D-3 score). First, we examined whether cognitive ability as measured by the MCCB Total score would mediate the relationship between anticholinergic burden and change in D-3 score, when controlling for age, gender, baseline performance on the D-3, psychiatric symptoms as measured by the PANSS Total score, and antipsychotic dose. Second, we examined whether MCCB also mediated an effect of dose (CPZeq) on change in D-3 score as an alternative to a specific effect of ACB. Third, we examined whether psychiatric symptoms as measured by the PANSS Total score would mediate the relationship between anticholinergic burden and change in D-3 score, controlling for age, gender, cognition as measured by the MCCB Total score, antipsychotic dose and baseline performance on the D-3. Fourth, we examined whether baseline functioning as measured by the SOFAS would mediate the relationship between anticholinergic burden and change in D-3 score, when controlling for age, gender, baseline performance on the D-3, cognition as measured by the MCCB Total score, psychiatric symptoms as measured by the PANSS Total score, and antipsychotic dose.

Table 2. Medications contributing to the anticholinergic cognitive burden (ACB) scale score

<table>
<thead>
<tr>
<th>Score of 1</th>
<th>No.</th>
<th>Score of 2</th>
<th>No.</th>
<th>Score of 3</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>10</td>
<td>Carbamazepine</td>
<td>1</td>
<td>Chlorpromazine</td>
<td>3</td>
</tr>
<tr>
<td>Captopril</td>
<td>1</td>
<td>Clomipramine</td>
<td>2</td>
<td>Clozapine</td>
<td>46</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>1</td>
<td>Olanzapine</td>
<td>34</td>
<td>Captopril</td>
<td>1</td>
</tr>
<tr>
<td>Codeine</td>
<td>1</td>
<td>Oxbutynin</td>
<td>3</td>
<td>Methadone</td>
<td>21</td>
</tr>
<tr>
<td>Frusenide</td>
<td>1</td>
<td>Paroxetine</td>
<td>1</td>
<td>Prednisolone</td>
<td>1</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>7</td>
<td>Procyclidine</td>
<td>21</td>
<td>Quinidine</td>
<td>3</td>
</tr>
<tr>
<td>Clozapine</td>
<td>46</td>
<td>Promethazine</td>
<td>1</td>
<td>Risperidone</td>
<td>9</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>1</td>
<td>Quetiapine</td>
<td>3</td>
<td>Quinidine</td>
<td>9</td>
</tr>
<tr>
<td>Codeine</td>
<td>1</td>
<td>Scopalamine</td>
<td>19</td>
<td>Tolterodine</td>
<td>2</td>
</tr>
<tr>
<td>Frusenide</td>
<td>1</td>
<td>Oxybutynin</td>
<td>3</td>
<td>Methadone</td>
<td>2</td>
</tr>
<tr>
<td>Methadone</td>
<td>2</td>
<td>Paroxetine</td>
<td>1</td>
<td>Prednisolone</td>
<td>1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>2</td>
<td>Procyclidine</td>
<td>21</td>
<td>Quinidine</td>
<td>3</td>
</tr>
<tr>
<td>Quinidine</td>
<td>1</td>
<td>Promethazine</td>
<td>1</td>
<td>Risperidone</td>
<td>9</td>
</tr>
<tr>
<td>Risperidone</td>
<td>9</td>
<td>Quetiapine</td>
<td>3</td>
<td>Tolterodine</td>
<td>2</td>
</tr>
</tbody>
</table>

Numbers (No.) are the numbers of patients receiving each medication. Note also that no patients were prescribed benzodiazepines.

![Diagram](image)

Fig. 1. C1, Direct effect of X on Y, before mediation via M; C2, direct effect of X on Y after mediation via M; A, indirect effect of X on Y mediated via M; B, direct effect of M on Y, adjusted for X.
antipsychotic dose, and psychiatric symptoms. Fifth, we examined whether cognition (MCCB Total score) would act as mediator when additionally controlling for baseline functioning (SOFAS), and whether baseline functioning (SOFAS) would act as a mediator when cognition (MCCB) was not controlled.

**Ethical standards**

This study was approved by the research ethics and effectiveness committee of the NFMHS and complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants gave written informed consent.

**Results**

**Magnitude of change over a 3-year period within a forensic mental health service**

The mean follow-up period (n = 70) was 2.94 years (s.d.=0.840). The mean change in D-3 score was −1.528 units (s.d. 5.22. This was a significant change [paired t = 2.448, df = 69, p < 0.017; 95% confidence interval (CI) 2.77–−0.28]. The Pearson correlation between baseline programme completion and programme completion at 3-year follow-up was r = 0.726. The magnitude of effect of 3 years of treatment in a forensic mental health service using D-3 was 0.295 (Cohen’s d).

**Anticholinergic burden and change in programme completion scores over 3 years**

The MCCB Total score completely mediated the relationship between anticholinergic burden (ACB) and the change in D-3 scores, when controlling for age, gender, baseline programme completion, total antipsychotic dose (CPZEq), and total psychopathology (PANSS). The unstandardized indirect effect of anticholinergic burden as measured by the ACB scale through cognition as measured using the MCCB Total score was −0.27 (95% CI −0.58 to −0.0545) (Table 3) which can be read that for every 1-point increase on the ACB scale changes on the D-3 decrease by −0.27 points.

**Cognition as a mediator between CPZEq and change in programme completion score**

To test the hypothesis that anticholinergic burden and not total antipsychotic dose had a specific effect on cognition which in turn influenced the functional outcome of programme completion we constructed a mediation model where CPZEq was the independent variable and controlled for anticholinergic burden.

### Table 3. Pearson correlations (n = 70) and significance (p) values

<table>
<thead>
<tr>
<th></th>
<th>ACB</th>
<th>MCCB Total</th>
<th>Change scores D-3</th>
<th>Baseline D-3</th>
<th>3 years D-3</th>
<th>PANSS Total</th>
<th>CPZEq</th>
<th>Baseline SOFAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACB</td>
<td>−</td>
<td>−0.547</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCCB Total</td>
<td>−</td>
<td>−0.290</td>
<td>0.290</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change scores D-3</td>
<td>−0.167</td>
<td>0.168</td>
<td>0.015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline D-3</td>
<td>0.340</td>
<td>−0.429</td>
<td>0.176</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Years follow-upD-3</td>
<td>0.414</td>
<td>−0.578</td>
<td>−0.516</td>
<td>0.735</td>
<td>−</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS Total</td>
<td>0.384</td>
<td>−0.403</td>
<td>−0.228</td>
<td>0.617</td>
<td>0.700</td>
<td>−</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPZEq</td>
<td>0.402</td>
<td>−0.250</td>
<td>−0.049</td>
<td>0.348</td>
<td>0.294</td>
<td>0.419</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Baseline SOFAS</td>
<td>−0.523</td>
<td>0.603</td>
<td>0.235</td>
<td>−0.719</td>
<td>−0.790</td>
<td>−0.631</td>
<td>−0.342</td>
<td></td>
</tr>
</tbody>
</table>

ACB, Anticholingeric Cognitive Burden scale; MCCB, Matrics consensus cognitive battery; Change scores D-3, DUNDRUM-3 Programme Completion Change Scale scores; Baseline D-3, DUNDRUM-3 Programme Completion Scale scores at baseline; 3 years follow-up D-3, DUNDRUM-3 Programme Completion Scale score at follow-up; PANSS, Positive and Negative symptom Scale; CPZEq, chlorpromazine equivalent; SOFAS, Social and Occupational Functioning Assessment Scale.
age, gender, psychopathology, and baseline programme completion. There was no evidence of a direct effect or an indirect effect via cognition for CPZeq on programme completion, when controlling for ACB and other variables.

**Total psychopathology as a mediator between anticholinergic burden and change scores for 3 years and programme completion**

To test the hypothesis that the effects of anticholinergic burden were specific to cognition and not psychopathology in general we constructed a model where PANSS Total score was the proposed mediator controlling for age, gender, baseline programme completion, CPZeq, and the MCCB Total score. There was no evidence of an indirect effect of PANSS Total score on change in D-3 score when controlling for other variables.

**SOFAS as a mediator between anticholinergic burden and change in programme completion scores over 3 years**

To test the hypothesis that the effect of anticholinergic burden was specific to cognition we constructed a mediation model where the effect of anticholinergic burden on change in D-3 score was mediated by social and occupational functioning (SOFAS) controlling for age, gender, baseline programme completion, MCCB Total Score, CPZeq, and PANSS Total score. Social and occupational functioning as measured by the SOFAS significantly mediated the relationship between ACB and change in programme completion but only when MCCB Total score was removed from the model.

**Cognition as a mediator between anticholinergic burden and change in programme completion scores when controlling for social and occupational functioning**

When controlling for social and occupational functioning at baseline the MCCB Total score no longer mediated ACB and change in D-3 scores (Table 4).

**Post-hoc analysis**

A *post-hoc* analysis exploring the mediation relationship between ACB, cognition (MCCB Total score) and disability or functioning (SOFAS) was also conducted, controlling for age, gender, psychopathology (PANSS Total) and medication (CPZeq). This analysis again used *PROCESS* and 10,000 bootstrapped samples. In total the model accounted for 59% of the variance of functioning (SOFAS). The direct effect of ACB on functioning (SOFAS) was not significant (−0.7657, 95% CI 9.6905). For every 1-point increase in anticholinergic burden score, functioning (SOFAS) declined by 1.4651 points.

This effect was specific to cognition being fully mediated by MCCB score. Psychopathology (PANSS Total) did not mediate the relationship between ACB and functioning when cognition was controlled for (−0.4508, 95% CI −1.558 to 0.4978). Further, the effect was specific to anticholinergic burden and not total antipsychotic dose. CPZeq did not affect functioning (SOFAS) via cognition, when ACB was controlled for (0.028, 95% CI −0.0026 to 0.0089).

**Discussion**

This is the first study to demonstrate that anticholinergic burden has a negative impact on the outcomes of psychosocial treatment programmes for patients with schizophrenia or schizoaffective disorder. It is noteworthy that many of the medications contributing to the ACB score were non-psychiatric. This adverse effect on psychosocial treatments appears to be mediated specifically through impaired cognitive capacity. The patients within this prospective cohort were cognitively impaired at baseline and had a mean MCCB *t* score composite of 21.3, which is almost 3 S.D. below the non-clinical mean. A score of this size approximates the cognitive abilities of individuals with a moderate intellectual disability. The cognitive ability of patients within this sample is especially marked given that their estimated premorbid IQ was found to be in the average range. Anticholinergic burden in part appeared to be a determinant of cognitive ability and psychosocial treatment outcomes. Within this study for every 1-unit increase on the ACB scale, patients change in D-3 scores, a scale measuring participation and benefit from psychosocial treatment programmes, decreased by −0.27 points. This decrease needs to be taken in context that the mean change score on the D-3 was 1.52 over the 3-year period (Cohen’s *d*=0.29). The range of change in D-3 score was, however, very wide (Table 1). Anticholinergic burden impairs cognition, which in turn impairs the ability to benefit from treatment programmes, even when controlling for a range of confounding variables including age, gender, antipsychotic dose and symptom severity.

These findings appear to be specific to anticholinergic burden and cognition. The effect of total antipsychotic dose on change in programme completion score was not mediated by cognition. Since no benzodiazepines were prescribed, these could not have contributed to slowed processing speed. Moreover, total psychopathology (PANSS) did not mediate the effect of anticholinergic burden on change in programme
## Table 4. Regression and mediation coefficients

### Model 1

<table>
<thead>
<tr>
<th>Mediator</th>
<th>$R^2$</th>
<th>p</th>
<th>Unstandardized effect size</th>
<th>95% CI</th>
<th>C1: direct effect of X on Y before mediation</th>
<th>Unstandardized effect size</th>
<th>95% CI</th>
<th>C2: direct effect of X on Y after mediation</th>
<th>Unstandardized effect size</th>
<th>A: indirect effect of X on Y mediated via M</th>
<th>Unstandardized effect size</th>
<th>95% CI</th>
<th>B: direct effect of M on Y adjusted for X</th>
<th>Unstandardized effect size</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>X = ACB</td>
<td>0.33</td>
<td>0.000</td>
<td>0.3653</td>
<td>−0.8555 to 0.1250</td>
<td>−0.0908</td>
<td>−0.6214 to 0.4397</td>
<td>−0.2744</td>
<td>−0.5897 to −0.0545</td>
<td>0.1104</td>
<td>0.0148 to 0.2060</td>
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<tr>
<td>M = MCCB</td>
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<td></td>
<td>0.1104</td>
<td>0.0148 to 0.2060</td>
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<td>Model 2</td>
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<td>0.1104</td>
<td>0.0148 to 0.2060</td>
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<tr>
<td>X = CPZeq</td>
<td>0.33</td>
<td>0.000</td>
<td>1.2032</td>
<td>−3.8297 to 6.2362</td>
<td>0.7165</td>
<td>−4.1716 to 5.6046</td>
<td>0.4867</td>
<td>−0.6244 to 2.4977</td>
<td>0.1104</td>
<td>0.0148 to 0.2060</td>
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<td>M = MCCB</td>
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<td>0.1104</td>
<td>0.0148 to 0.2060</td>
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<td>Model 3</td>
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<td>0.1104</td>
<td>0.0148 to 0.2060</td>
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<tr>
<td>X = ACB</td>
<td>0.33</td>
<td>0.000</td>
<td>−0.2236</td>
<td>−0.7837 to 0.3364</td>
<td>−0.0908</td>
<td>−0.6214 to 0.4397</td>
<td>−0.1328</td>
<td>−0.4043 to 0.0624</td>
<td>−0.0989</td>
<td>−0.1612 to −0.0365</td>
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<tr>
<td>M = PANSS</td>
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<td>0.1104</td>
<td>0.0148 to 0.2060</td>
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<td>0.0148 to 0.2060</td>
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<tr>
<td>X = ACB</td>
<td>0.41</td>
<td>0.000</td>
<td>−0.0908</td>
<td>−0.6214 to 0.4397</td>
<td>0.0529</td>
<td>−0.4555 to 0.5612</td>
<td>−0.1437</td>
<td>−0.4033 to 0.0244</td>
<td>0.1242</td>
<td>0.0416 to 0.2067</td>
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<td>M = SOFAS</td>
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<td>0.0148 to 0.2060</td>
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<td>Model 5</td>
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<td>0.1104</td>
<td>0.0148 to 0.2060</td>
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<tr>
<td>X = ACB</td>
<td>0.41</td>
<td>0.000</td>
<td>−0.0761</td>
<td>−0.5538 to 0.4017</td>
<td>0.0529</td>
<td>−0.4555 to 0.5612</td>
<td>−0.1289</td>
<td>−0.3904 to 0.0308</td>
<td>0.0666</td>
<td>−0.0280 to 0.1611</td>
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<tr>
<td>M = MCCB</td>
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<td>0.0148 to 0.2060</td>
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<td>Model 6</td>
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<td>0.1104</td>
<td>0.0148 to 0.2060</td>
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<tr>
<td>X = ACB</td>
<td>0.34</td>
<td>0.0002</td>
<td>−0.3653</td>
<td>−0.8555 to 0.1250</td>
<td>−0.0761</td>
<td>−0.5538 to 0.4017</td>
<td>−0.2892</td>
<td>−0.6079 to −0.0674</td>
<td>0.1421</td>
<td>0.0630 to 0.2212</td>
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<tr>
<td>M = SOFAS</td>
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<td>0.1104</td>
<td>0.0148 to 0.2060</td>
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CI, Confidence interval; ACB, Anticholinergic Cognitive Burden scale; MCCB, Matrics consensus cognitive battery; CPZeq, chlorpromazine equivalent; PANSS, Positive and Negative Symptom Scale; SOFAS, Social and Occupational Functioning Assessment Scale.

In all cases, the outcome (Y) is ‘Change in DUNDRUM-3 Programme Completion Scale scores’. X is the hypothesized determinant factor and M is the hypothesized mediating factor. Total sample $n = 70$.

Models 1, 2, 3 include age, gender, DUNDRUM-3 Programme Completion Scale (D-3) baseline scores; PANSS Total, MCCB Total, and CPZeq. Models 4 and 5 also include SOFAS in addition to age, gender, D-3 Baseline, PANSS Total, MCCB Total and CPZeq. Model 6 does not include or control for MCCB and contains ACB, SOFAS, age, gender, PANSS Total, and CPZeq. In each case the dependent variable (Y) is change scores on the D-3.
Anticholinergic burden in schizophrenia and psychosocial treatment programmes

Clinicians’ ratings of patients’ psychosocial and occupational functioning (SOFAS) also did not mediate the relationship between anticholinergic burden and change in programme completion when cognition was controlled for. But SOFAS did mediate the relationship between anticholinergic burden and programme completion when cognitive ability was removed from the model, presumably because functioning is in part dependent on cognitive capacity.

Our post-hoc analysis demonstrates that anticholinergic burden may impact on patient disability as measured by the SOFAS. This effect again is specific to cognition as demonstrated by mediation analysis. Mediation analysis also shows that the effect of ACB on SOFAS is specific to anticholinergic burden and not total antipsychotic dose (CPZeq). This may have implications for rehabilitation in schizophrenia.

The findings of this study may go some way to explaining why Wunderink et al. (2013) found that dose reduction of antipsychotic medication was linked with superior functional but not symptomatic remission in comparison to maintenance treatment at 7 years follow-up. Reductions in anticholinergic burden may have been the mechanism responsible for this improved psychosocial functioning. It has been suggested that treatments like CBT may not be as helpful for patients with schizophrenia as for some other problems (Jauhar et al. 2014). But psychological interventions have a robust evidence base for a range of disorders (Carr, 2009). One reason for reduced efficacy in schizophrenia may be that cognitive impairments affect patients’ ability to attend to, process, store, and use the information offered during psychological interventions (Green et al. 2000; Kurtz, 2011). This study illuminates a possible iatrogenic effect that pharmacotherapy can have on cognition and functioning, which in turn affects the outcome of psychosocial treatment. Cognitive ability and anticholinergic burden should therefore routinely be considered as moderators in clinical trials of psychological therapy for patients with schizophrenia.

We do not propose that anticholinergic burden is the sole cause of cognitive impairments amongst patients with schizophrenia or even the major cause, because these difficulties have been observed in medication naïve patients (Kahn & Keefe, 2013). However our findings do suggest that anticholinergic burden may have adverse effects for patients with schizophrenia. There are studies suggesting that there is a widespread decrease in muscarinic receptors in the brains of people with schizophrenia (Scarr et al. 2013) including post-mortem studies (Mancama et al. 2003; Zavitsanou et al. 2004; Newell et al. 2007; Gibbons et al. 2013) and a brain-imaging study (Raedler et al. 2003). Similar to older patients, or those with dementia, people with schizophrenia are likely to have a vulnerable brain with a paucity of cholinergic neurons (Tune, 2001; Campbell et al. 2009; van Haren et al. 2011; Harvey & Bowie, 2012; Kahn et al. 2015; Gray et al. 2015; Kubota et al. 2015). Physicians are therefore required to conduct careful risk benefit decisions and collaborate with patients regarding the medications they prescribe. The ACB scale may be a useful clinical tool for helping physicians and patients make these decisions. Because verbal intelligence in people with schizophrenia is largely intact (Michel et al. 2013), it may be particularly challenging for physicians to identify declines or impairments in other cognitive domains. Also cognitive screening instruments may not be helpful as they do not take account of a patient’s premorbid intellectual ability or have enough sensitivity to change (Lezak et al. 2012). Therefore comprehensive neuropsychological assessment using psychometrically robust and functionally relevant instruments may be important in the planning of care and treatment for people with schizophrenia.

This study has a number of methodological strengths as well as limitations. Strengths include a sample made up of most of a national cohort of forensic patients diagnosed with schizophrenia or schizoaffective disorder. This sample was followed up over a 3-year period. The use of the MCCB measure for assessing cognitive problems in schizophrenia and controlling for a range of confounders including psychopathology and antipsychotic dose are also strengths. Furthermore, all measurements were conducted independently of each other.

Limitations in this study include the specialist sample consisting entirely of forensic patients which may raise questions regarding the generalizability of the results to other samples of patients with schizophrenia. Patient participation and benefit from psychosocial treatment programmes was measured using the D-3 which has been specifically developed and recommended for this patient group. This scale takes account of the wide range of psychosocial interventions provided for hospitalized patients over a 3-year period. Because no attempt is made here to distinguish between treatment responses to different treatment programmes, the overall effect measured is a measure of ‘treatment as usual’ with multi-disciplinary delivery of programmes. The sample in this study was cross-sectional rather than an incident series of new admissions. To achieve an incident sample of sufficient size, a very prolonged study over as much as a decade would have been required, or a multi-centre study.

This study supports the validity of the ACB scale given its correlations with the MCCB, SOFAS, and D-3. However it is important to point out that a number of criticisms have been levelled at anticholinergic burden scales. There is no consensus for how to
calculate anticholinergic burden. Although a bioassay of serum anticholinergic activity has in the past been considered the gold standard it is only a marker of anticholinergic activity in serum, and not in the brain (Hori et al. 2014). Also dosage is not considered within clinical scales such as the ACB and medications are unlikely to have a simple 0:1:2:3 ratio in relation to dose or in relation to each other. However, a number of studies have found that unit weighting as used in the ACB scale is quite robust for making predictions (Dawes, 1979). Unit weighting performs particularly well where the criterion (in this case central anticholinergic effect) cannot be quantified and this is precisely the case regarding anticholinergic burden (Dawes, 1979). Unit weighting also performs well when there is not a straightforward relationship between the predictor variables and the criterion (Dawes, 1979), and there is considerable individual variation in absorption, distribution, rate of metabolism, formation, and excretion of pharmacologically active metabolites (Pollock, 2000). A third criticism of anticholinergic scales is that there is variability in the quantification of anticholinergic burden across different instruments. However, unit weighting is also viable when it is difficult to develop a regression model because of a larger number of predictors. There are more than 600 medications that have anticholinergic activity (Chew et al. 2008). Finally, because medications with anticholinergic properties do not have a straightforward relationship with cognitive decline the correlation between scales may be a better measure of construct validity than the kappa coefficient (Lertxundi et al. 2013).

Although a number of confounding factors were controlled for there was no attempt to manipulate any variable and therefore the study only approximates a causal design. The value of this study is that it establishes a case for an intervention study using meaningful outcome measures concerning treatment engagement and response, and real world functional outcomes. A number of studies have suggested that discontinuing anticholinergic treatments had a positive effect on cognition among patients with schizophrenia (Baker et al. 1983; Mori et al. 2002; Drimer et al. 2004; Ogino et al. 2011; Desmarais et al. 2014). But no study has yet examined whether improvements in cognition following reduction in anticholinergic burden have in turn affected real-world functioning.

Conclusion

Anticholinergic burden as measured by the ACB scale had a significant impact on patient ability to participate and benefit from psychosocial treatments within a forensic hospital as measured by change in D-3 score. Anticholinergic burden appears to impair cognitive ability and real-world functioning, which in turn affects patient ability to participate in and benefit from psychosocial programmes. Physicians need to be mindful of the cumulative effect that psychiatric and other medications can have on cognitive ability, functional capacity, and ability to participate and benefit from psychosocial treatments.

Acknowledgements

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Declaration of Interest

None.

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