Mortality in schizophrenia

Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study

JOHN L. WADDINGTON, HANAFY A. YOUSSEF and ANTHONY KINSELLA

Background Although increased mortality is one of the most consistent and accepted epidemiological findings in schizophrenia, a high rate of suicide appears unable to account fully for this burden which remains poorly understood.

Method A cohort of 88 in-patients was followed prospectively over a 10-year period and predictors of survival sought among demographic, clinical and treatment variables.

Results Over the decade, 39 of the 88 patients (44%) died, with no instances of suicide. Reduced survival was predicted by increasing age, male gender, edentulousness and time since pre-terminal withdrawal of antipsychotics; additionally, two indices of polypharmacy predicted reduced survival: maximum number of antipsychotics given concurrently (relative risk 2.46, 95% CI 1.10–5.47; \( P = 0.03 \)) and absence of co-treatment with an anticholinergic (relative risk 3.33, 95% CI 0.99–11.11; \( P = 0.05 \)).

Conclusions Receiving more than one antipsychotic concurrently was associated with reduced survival, in the face of little or no systematic evidence to justify the widespread use of antipsychotic polypharmacy. Conversely, over-cautious attitudes to the use of adjunctive anticholinergics may require re-evaluation.

Although there endures intense debate as to its aetiology and pathophysiology (Waddington, 1993; Weinberger, 1995), excess mortality in schizophrenia is one of the most consistent and accepted epidemiological findings (Jablensky, 1995); in the context of a disorder having a lifetime prevalence of 0.5–1.0% and a relative overall mortality more than twice that of the general population, this premature loss of life is both substantial and poorly understood (Brown, 1997). It is widely recognised that high levels of suicide are not confined to affective disorder, with up to 10% of patients with schizophrenia taking their own life (Caldwell & Gottesman, 1990); however, this high rate of suicide appears unable to account fully for the excess burden of mortality (Jablensky, 1995; Brown, 1997). Thus, attention has been directed to whether sufferers might also be at increased risk for physical disease. At least one additional factor has a potential role in the early demise of some patients with schizophrenia, namely the antipsychotic drugs that are now used ubiquitously in their treatment. Use of these agents has been a cause of periodic concern in relation to instances of sudden, unexpected death in psychotic patients receiving such medication, particularly at higher doses (Working Group of the Royal College of Psychiatrists, Psychopharmacology Sub-Group, 1997) and in patients receiving lower doses in the context of particular neuropsychiatric disorders (McKeith et al., 1992). Any impact on survival of very long-term exposure to antipsychotics has received little attention. Furthermore, there are no contemporary long-term prospective studies that have addressed these issues. Since the 1980s, we have been conducting a long-term prospective study in a sample of chronically ill in-patients with schizophrenia; these patients were evaluated in detail at study entry for multiple demographic, clinical and medication variables (Waddington et al., 1987) and have been followed longitudinally thereafter (Waddington et al., 1990, 1995). Very specific information on the circumstances of each death was therefore available. The objective of the present study was to identify predictors of reduced survival over a 10-year period in circumstances that allowed isolation of non-suicide-related or other non-natural causes.

METHOD

Subjects

In 1983, we identified (Waddington et al., 1987) a sample of 101 in-patients who satisfied Washington University criteria for a diagnosis of schizophrenia among those resident in the then seven wards of St Davnet’s Hospital, Monaghan, a long-term psychiatric care facility in rural Ireland which services the Cavan–Monaghan catchment area. The records of these 101 in-patients were reviewed to document the following demographic variables: age, gender, age at onset (defined by first contact with a psychiatric service, usually first admission) and duration of illness.

Demographics

It was also possible to obtain from these records an unusually detailed history of drug treatment because of several factors particular to such a rural Irish population (Waddington et al., 1987). The vast majority of patients had received all of their psychiatric care, often extending over several decades, in St Davnet’s. Furthermore, this cultural feature of life in rural Ireland extended also to the physicians in charge of these patients’ care, since psychiatrists usually remained in post for prolonged periods, providing continuity of records. The efficiency of the nursing staff in keeping together all documentation relating to each patient contributed further to this atypically rich database of decades of drug treatment. From this, it was possible to determine the following medication variables: age at first antipsychotic treatment; total duration of antipsychotic treatment; average daily dose of antipsychotics over that duration, in chlorpromazine equivalents (CPZ eq); lifetime intake of antipsychotics in CPZ eq; daily dosage of antipsychotics on day of assessment in CPZ eq; duration of intramuscular depot antipsychotic treatment; number of different antipsychotics given over total duration.
of treatment; maximum number of antipsychotics given concurrently; duration of antipsychotic polypharmacy (i.e. two or more antipsychotics given concurrently); time since most recent withdrawal of antipsychotic treatment if not currently in receipt; number of interruptions to antipsychotic treatment longer than one month since first given antipsychotics; total time antipsychotic-free since first given antipsychotics; total duration of treatment with anticholinergics; presence or absence of anticholinergics on the day of assessment.

As previously described in detail (Waddington et al, 1987), patients who consented to participate in the study were assessed clinically for psychopathology, focusing among this prominently negatively symptom-laden group on operationalised indices of flattening of affect, poverty of speech and cognitive impairment, for tardive dyskinesia, and for absence of teeth (edentulousness).

Mortality

Over the 10-year prospective period, 1983–1993, details on each patient death were obtained from three sources: the patient’s case records, the hospital ‘death-book’, and the official death certificate as obtained from the General Register Office of the Department of Health, Ireland. Where necessary, this information was supplemented by interviews with health professionals who attended the death. Causes of death were classified in accordance with the ICD–9 (World Health Organization, 1978).

Data analysis

Mortality data for the patient population using the primary end point of age at death from any cause, were analysed actuarially by the life table method using the 1992 Statistical Release, subsequent to the 1991 Census of Population, from the Central Statistics Office, Government Information Service, Ireland. Relative risk was determined as the observed number of deaths divided by the expected number of deaths, adjusting for age and gender, together with 95% confidence intervals and two-tailed probability values as calculated using exact methods (Epi-Info 6.02).

Survival data for the patient population, as individual times from initial evaluation in 1983 to death, and with those still alive in 1993 treated as censored observations, were analysed by Cox proportional hazards modelling (BMDP statistical software package); those variables in the 1983 data set which made a significant independent prediction of hazard ratio were identified in terms of their model coefficients and associated relative risk, together with 95% confidence intervals and two-tailed probability values.

RESULTS

Complete data on all study variables were available for 88 of the 101 patients; their demographic and medication characteristics are given in Table 1, with clinical characteristics as described previously in detail (Waddington et al, 1987, 1990, 1995). For eight patients, case records did not document treatment or were otherwise incomplete, while five patients declined to participate in the study; the mean age (65.5 years (s.d.=16.7)) and mortality (seven of 13 deceased over the 10-year period) of these missing cases did not differ significantly from the 88 patients who entered data analysis.

In the course of this 10-year prospective period, 39 of the 88 patients had died, all except one (a post-mortem-confirmed myocardial infarction in an in-patient who had wandered) in hospital; an expected value of 29.4 indicated a relative risk of 1.33 with 95% confidence interval of 1.01–1.65 (P=0.03). There were no instances of suicide among this older, in-patient population showing predominantly the negative symptoms of schizophrenia, and all deaths except one were from evident natural causes; in this one instance of possible 'unnatural death', the patient was kicked in the groin area by a fellow patient and transferred to the regional hospital, where he died a few days later from generalised peritonitis (gram-negative bacteraemia) in the course of treatment for perforated diverticulum of the sigmoid colon.

Causes of death among 39 deceased patients were quantified in terms of those groupings of principal causes (ICD–9 criteria) among the general population as utilised in the Report on Vital Statistics, Department of Health, Ireland (Department of Health, 1995); percentage distribution of causes of death among the patients (with general population figures) were as follows: circulatory disease 41.0% (44.9%); malignant disease 7.7% (23.8%); respiratory disease 25.6% (13.7%); injury and poisoning 2.6% (4.3%); all other causes 23.1% (13.1%).

Cox proportional hazards modelling identified six variables as effecting independent prediction of reduced survival among the 88 patients: increasing age, male gender, edentulousness, time since most recent withdrawal of antipsychotics, maximum number of antipsychotics given concurrently, and duration of antipsychotic treatment longer than one month since first given antipsychotics; total time antipsychotic-free since first given antipsychotics; total duration of treatment with anticholinergics; presence or absence of anticholinergics on the day of assessment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>62.6 (13.4) 25–89</th>
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<tbody>
<tr>
<td>Age, years (mean (s.d.) range)</td>
<td>Age at onset, years (mean (s.d.) range)</td>
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<tr>
<td>Duration of illness, years (mean (s.d.) range)</td>
<td>27.9 (9.6) 14–66</td>
</tr>
<tr>
<td>Age at first antipsychotic treatment, years (mean (s.d.) range)</td>
<td>34.6 (11.5) 7–61</td>
</tr>
<tr>
<td>Duration of antipsychotic treatment, years (mean (s.d.) range)</td>
<td>45.0 (14.6) 18–83</td>
</tr>
<tr>
<td>Average daily dose of antipsychotics over duration, mg CPZ eq (mean (s.d.) range)</td>
<td>15.0 (6.9) 0.2–26.7</td>
</tr>
<tr>
<td>Lifetime intake of antipsychotics, g CPZ eq (mean (s.d.) range)</td>
<td>305 (273) 48–1853</td>
</tr>
<tr>
<td>Current daily dose of antipsychotics, mg CPZ eq (mean (s.d.) range)</td>
<td>1709 (1705) 3–10115</td>
</tr>
<tr>
<td>Number of different antipsychotics given over duration (mean (s.d.) range)</td>
<td>546 (1302) 0–8600</td>
</tr>
<tr>
<td>Maximum number of antipsychotics given concurrently (mean (s.d.) range)</td>
<td>3.8 (2.0) 1–9</td>
</tr>
<tr>
<td>Duration of antipsychotic polypharmacy, years (mean (s.d.) range)</td>
<td>1.0 (0.6) 1–3</td>
</tr>
<tr>
<td>Time antipsychotic-free over duration of treatment, years (mean (s.d.) range)</td>
<td>4.3 (4.8) 0–18.5</td>
</tr>
<tr>
<td>Time since most recent withdrawal of antipsychotics, years (mean (s.d.) range)</td>
<td>2.5 (3.7) 0–14.4</td>
</tr>
<tr>
<td>Duration of treatment with anticholinergics, years (mean (s.d.) range)</td>
<td>1.2 (2.7) 0–12.3</td>
</tr>
<tr>
<td>Current treatment with anticholinergics (prevalence %)</td>
<td>6.2 (5.0) 0–17.1</td>
</tr>
<tr>
<td>Edentulousness (prevalence %)</td>
<td>26.88 (30%)</td>
</tr>
<tr>
<td>Tardive dyskinesia (prevalence %)</td>
<td>37.88 (42%)</td>
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</tbody>
</table>

Table 1 Characteristics of the 88 patients (50 men, 38 women) at entry into the prospective study

CPZ eq, chlorpromazine equivalents.
The primary purpose of the present study was to identify predictors of reduced survival among a population of patients with schizophrenia who had been evaluated in detail on several dimensions at study entry and then followed prospectively over 10 years by the same investigatory team, and for whom suicide could be excluded as a cause of death. The population consisted of long-term in-patients from a region of rural Ireland that demonstrates substantial ethnic and socio-economic homogeneity, who had each experienced essentially all of their illness and medical care within this one psychiatric hospital, and who were therefore also homogeneous for factors such as physical environment, social structure and diet; thus, they constitute a rare and powerful opportunity to study predictors of reduced survival in schizophrenia under substantially uniform conditions for which it would be otherwise difficult to control.

**DISCUSSION**

**Mortality in schizophrenia**

In this prospective study of mortality in schizophrenia, we were able to obviate the impact of suicide or other ‘unnatural’ causes of death, an often distressingly high contributor to overall mortality particularly among younger patient populations (Caldwell & Gottesman, 1990; Jablensky, 1995; Brown, 1997) but a serious confound in defining the contribution of physical illness. The findings indicated among older in-patients a 33% increase in risk for ‘natural’ death over a 10-year period. Although not a specific focus of the present study, inspection of causes of death in the present patient population relative to general population data suggested an under-representation of malignant disease, consistent with some studies in a controversial body of literature, but an overrepresentation of respiratory and other non-circulatory disease, in accordance with several previous reports in younger and older, out-patient populations (Licht et al, 1993; Saku et al, 1995; Brown, 1997).

The findings gave very similar results.

**General predictors of survival**

As expected, the primary predictor of reduced survival was increasing age, with males at greater risk than females; importantly, these findings indicate that the present methods as applied to the present study population are capable of revealing those fundamental aspects of general population mortality that are evident on a worldwide basis. Edentulousness appeared to predict reduced survival as a proxy for a process of global physical, mental and behavioural deterioration that appears to characterise many older, chronically ill people with schizophrenia (Waddington et al, 1987), as manifest as an increase in poor dental hygiene which may predispose to respiratory infection (Yoneyama et al, 1996); it was evaluated in the context of assessments for tardive (orofacial) dyskinesia, no index of which was associated with increased risk. Similarly, increasing time since final withdrawal of antipsychotics appeared to predict reduced survival as a proxy for the chronicity of terminal physical illness that replaced psychiatric disorder as the primary focus of medical care.

**Antipsychotic polypharmacy**

The other two variables found to be associated with increased risk are potential causes of concern and present the greatest challenge. The greater the maximum number of antipsychotics given concurrently, the shorter was patient survival. At the outset, it is necessary to consider the extent to which an increasing number of concurrent antipsychotics might be a proxy for severity/refractoriness of psychiatric illness, with lack of adequate response to a single agent prompting recourse to co-administration of a second or third antipsychotic; severity/refractoriness of illness would then be in some way the ‘cause’ of reduced survival. While such a process would itself be of considerable interest in relation to a ‘whole-body’ concept of schizophrenia and cannot be excluded, such an explanation does not appear straightforward for the following reasons: first, no other equally viable index of increasing co-medication, such as average daily dose of antipsychotics given over total duration of exposure or lifetime intake of antipsychotics, predicted risk; second, there was no such relationship to the number of different antipsychotics given over the total duration of exposure, that is, the important factor was being in receipt of more than one antipsychotic concurrently even in the face of being exposed on average to a considerably larger number of different antipsychotics sequentially; third, no measured index of illness severity, focusing particularly on those negative symptom and cognitive domains of psychopathology which indicate greatest long-term severity and are most refractory to antipsychotics (Kane, 1996), was associated with reduced survival. Furthermore, if inadequate response to a single agent were the sole basis for antipsychotic polypharmacy, it would be remarkable that simple addition of the number of antipsychotics given concurrently was a more reliable index of illness severity than any direct measure of symptoms and outcome. Rather, antipsychotic polypharmacy appeared to occur for several independent reasons beyond inadequate response to a

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### Table 2 Predictors of reduced survival by Cox proportional hazards modelling

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>s.e.β</th>
<th>P</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.09</td>
<td>0.03</td>
<td>&lt;0.001</td>
<td>1.10</td>
<td>1.04-1.16</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.79</td>
<td>0.45</td>
<td>0.07</td>
<td>2.21</td>
<td>0.92-5.30</td>
</tr>
<tr>
<td>Edentulousness</td>
<td>0.81</td>
<td>0.41</td>
<td>0.05</td>
<td>2.26</td>
<td>1.01-5.03</td>
</tr>
<tr>
<td>Time since final withdrawal</td>
<td>0.13</td>
<td>0.07</td>
<td>0.05</td>
<td>1.14</td>
<td>1.00-1.30</td>
</tr>
<tr>
<td>of antipsychotics, years</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Maximum number of antipsychotics</td>
<td>0.90</td>
<td>0.41</td>
<td>0.03</td>
<td>2.46</td>
<td>1.10-5.47</td>
</tr>
<tr>
<td>given concurrently</td>
<td></td>
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<tr>
<td>Absence of anticholinergic treatment</td>
<td>1.20</td>
<td>0.62</td>
<td>0.05</td>
<td>3.33</td>
<td>0.99-11.11</td>
</tr>
</tbody>
</table>
single agent, including the common prac-
tice of administering a sedative pheno-
thiamine nocte to facilitate sleep, on a
background of an oral or depot antipsy-
chotic, and physician preference for an
‘incise’ oral antipsychotic on a back-
ground of a depot antipsychotic; indeed,
individual antipsychotic combinations and
their bases were so heterogeneous as to
preclude systematic analysis.

An alternative interpretation is that
some adverse biological consequence(s) of
receiving more than one antipsychotic
concurrently can lead to reduced survival.
Antipsychotics, particularly the classical
neuroleptics administered to the present
population, influence a wide range of
biological mechanisms over the whole of
the body, in addition to their presumed
primary action as antagonists of brain D2
dopamine receptors. These include inter-
actions with numerous non-dopaminergic
receptors in diverse physiological systems
and, at higher doses, effects on more
fundamental cellular processes (Wadding-
ton, 1992, 1995; Kane, 1996). Instances of
sudden, unexpected death following acute
administration of high doses of classical
neuroleptics has engendered considerable
concern, particularly in relation to adverse
cardiowascular sequelae (Working Group of
the Royal College of Psychiatrists, Psych-
opharmacology Sub-Group, 1997); addi-
tional and more gradual adverse effects
may be recruited when lower doses of
classical neuroleptics are given for some-
what longer periods (Waddington, 1992),
and this would be more likely when more
than one is given concurrently. The breadth
of the physiological effects of classical
neuroleptics appear to increase risk for
death or ‘near death’ among patients with
psychosis and asthmatic conditions (Joseph
et al., 1996). Although the relationship
between antipsychotic polypharmacy and
reduced survival remains open to interpre-
tations other than an increasing burden of
physiological dysfunction due to multiple
drug effects, it should be emphasised that
there is little or no systematic evidence for
antipsychotic polypharmacy in schizo-
phrenia being any more effective than
monotherapy (Dufresne, 1995; Kane,
1995; Naftadowitz et al., 1995); thus, con-
sideration of the present association with
the practice of antipsychotic polypharmacy
must be juxtaposed with lack of any
empirical evidence to justify that practice,
despite it being adopted on a widespread
basis.

CLINICAL IMPLICATIONS

- Antipsychotic polypharmacy associated with reduced survival over a 10-year prospective period.
- Absence of adjunctive anticholinergics also associated with reduced survival.
- Little or no systematic evidence to justify antipsychotic polypharmacy.

LIMITATIONS

- The study involved a modest number of cases followed prospectively.
- Uncertainty as to generalisability, particularly outside of in-patient populations.
- Status of atypical antipsychotics remains unknown.

Anticholinergic usage

The absence of adjunctive anticholinergic
treatment was associated with reduced
survival. A debate has endured since the
1960s as to whether anticholinergics
should be administered routinely with
classical neuroleptics or given only for
overt extrapyramidal side-effects. A recent
World Health Organization consensus
statement (World Health Organization,
1990) concluded that prophylactic use of
anticholinergics in patients receiving neu-
roleptics was not to be recommended,
though the issue is highly complex
(Barnes, 1990; Kane, 1996). In the ab-

Anthropological considerations

At an anthropological level, life-span in
primate species, including humans, is pro-
portional to brain volume, after correcting
for differences in body weight; in particu-
lar, volume of the amygdala shows the
most consistent association with life-span
(Allman et al., 1993). There is evidence for
reduced brain volume in schizophrenia
relative to normal subjects, including
reductions in the hippocampal/amygdala

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