Mortality in schizophrenia

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

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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

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

Characteristic	
Age, years (mean (s.d.) range)	62.6 (13.4) 25–89
Age at onset, years (mean (s.d.) range)	27.9 (9.6) 14–66
Duration of illness, years (mean (s.d.) range)	34.6 (11.5) 7–61
Age at first antipsychotic treatment, years (mean (s.d.) range)	45.0 (14.6) 18–83
Duration of antipsychotic treatment, years (mean (s.d.) range)	15.0 (6.9) 0.2–26.7
Average daily dose of antipsychotics over duration, mg CPZ eq (mean (s.d.) range)	305 (273) 48–1853
Lifetime intake of antipsychotics, g CPZ eq (mean (s.d. range)	1709 (1705) 3–10 115
Current daily dose of antipsychotics, mg CPZ eq (mean (s.d.) range)	546 (1302) 0–8600
Number of different antipsychotics given over duration (mean (s.d.) range)	3.8 (2.0) 1–9
Maximum number of antipsychotics given concurrently (mean (s.d.) range)	1.8 (0.6) 1–3
Duration of antipsychotic polypharmacy, years (mean (s.d.) range)	4.3 (4.8) 0–18.5
Time antipsychotic-free over duration of treatment, years (mean (s.d.) range)	2.5 (3.7) 0–14.4
Time since most recent withdrawal of antipsychotics, years (mean (s.d.) range)	1.2 (2.7) 0–12.3
Duration of treatment with anticholinergics, years (mean (s.d.) range)	6.2 (5.0) 0–17.1
Current treatment with anticholinergics (prevalence (%))	26/88 (30%)
Edentulousness (prevalence (%))	33/88 (38%)
Tardive dyskinesia (prevalence (%))	37/88 (42%)

CPZ eq, chlorpromazine equivalents.

concurrently, and absence of anticholinergic treatment (Table 2); repeating the Cox regression analysis in a step-wise manner generated a very similar set of predictors. No other variables effected significant prediction of reduced survival ($P > 0.15$). To examine whether the one instance of possible 'unnatural death' might be exerting a disproportionate influence on the findings, analysis was repeated with this case deleted; among the remaining 87 patients, Cox proportional hazards modelling gave very similar results.

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 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.

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 manifested inter alia 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) dyskine-

sia, 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

Table 2 Predictors of reduced survival by Cox proportional hazards modelling

Variable	β	s.e.β	P	Relative risk	95% CI
Age, years	0.09	0.03	<0.001	1.10	1.04–1.16
Male gender	0.79	0.45	0.07	2.21	0.92–5.30
Edentulousness	0.81	0.41	0.05	2.26	1.01–5.03
Time since final withdrawal of antipsychotics, years	0.13	0.07	0.05	1.14	1.00–1.30
Maximum number of antipsychotics given concurrently	0.90	0.41	0.03	2.46	1.10–5.47
Absence of anticholinergic treatment	1.20	0.62	0.05	3.33	0.99–11.11

single agent, including the common practice of administering a sedative phenothiazine *nocte* to facilitate sleep, on a background of an oral or depot antipsychotic, and physician preference for an 'incisive' oral antipsychotic on a background 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 D_2 dopamine receptors. These include interactions with numerous non-dopaminergic receptors in diverse physiological systems and, at higher doses, effects on more fundamental cellular processes (Waddington, 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 cardiovascular sequelae (Working Group of the Royal College of Psychiatrists, Psychopharmacology Sub-Group, 1997); additional and more gradual adverse effects may be recruited when lower doses of classical neuroleptics are given for somewhat 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 interpretations 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 schizophrenia being any more effective than monotherapy (Dufresne, 1995; Kane, 1995; Naftdowitz *et al*, 1995); thus, consideration 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.

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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 neuroleptics was not to be recommended, though the issue is highly complex (Barnes, 1990; Kane, 1996). In the absence of any direct assessment of extrapyramidal side-effects such as Parkinsonism in the present study, interpretation of the association must be cautious. Nevertheless, patients who are being treated with neuroleptics in the absence of an adjunctive anticholinergic may be more likely than those in receipt of an anticholinergic to manifest sub-clinical Parkinsonism features at the level of more subtle diminution in motor function. In this context, it is notable that several recent studies have found a lower level of activity to be associated with reduced survival among older members of the general population, in accordance with an 'activity theory' formulation of mortality prediction (Stones *et al*, 1989; Ratowski & Mor, 1992). Though not without potential liabilities at other levels (World Health Organization, 1990; Barnes, 1990), re-evaluation of possibly overcautious attitudes to judicious use of anticholinergics, particularly among older patients receiving neuroleptics, might help to mitigate the 'low activity propensity' that appears to exert an adverse impact on general life expectancy; furthermore, it is difficult to conceptualise neuroleptic polypharmacy as other than exacerbating such a propensity.

Anthropological considerations

At an anthropological level, life-span in primate species, including humans, is proportional to brain volume, after correcting for differences in body weight; in particular, 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

region (Waddington, 1993; Weinberger, 1995); hence, in schizophrenia there may be some fundamental relationship between reduced survival and reduced brain volume. It is on this substrate that additional factors, such as those associated with antipsychotic polypharmacy and lack of adjunctive anticholinergics, may act to modulate survival. The extent to which new, atypical antipsychotics might show a similar or reduced association in this regard awaits study.

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REFERENCES

Allman, J., McLaughlin, T. & Hakeem, A. (1993) Brain structures and life-span in primate species. *Proceedings of the National Academy of Sciences USA*, **90**, 3559–3563.

Barnes, T. R. E. (1990) Comment on the WHO consensus statement. *British Journal of Psychiatry*, **156**, 413–414.

Brown, S. (1997) Excess mortality of schizophrenia. A meta-analysis. *British Journal of Psychiatry*, **171**, 502–508.

Caldwell, C. B. & Gottesman, I. I. (1990) Schizophrenics kill themselves too: a review of risk factors for suicide. *Schizophrenia Bulletin*, **16**, 571–589.

Department of Health (1995) *Health Statistics 1993.* Dublin: Stationery Office, Government of Ireland.

Dufresne, R. L. (1995) Psychiatric pharmacy research workshop: Issues in polypharmacotherapy. *Psychopharmacology Bulletin*, **31**, 789–796.

Jablensky, A. (1995) Schizophrenia: the epidemiological horizon. In *Schizophrenia* (eds S. R. Hirsch & D. R. Weinberger), pp. 206–252. Oxford: Blackwell.

Joseph, K. S., Blais, L., Ernst, P., et al (1996) Increased morbidity and mortality related to asthma among asthmatic patients who use major tranquillisers. *British Medical Journal*, **312**, 79–83.

Kane, J. M. (1995) Psychopharmacological approaches to schizophrenia: practical aspects. In *Advances in the Neurobiology of Schizophrenia* (eds J. A. Den Boer, H. G. M. Westenberg & H. M. Van Praag), pp. 245–263. Chichester: Wiley.

__ **(1996)** Drug therapy: schizophrenia. *New England Journal of Medicine*, **334**, 34–41.

Licht, R. W., Mortensen, P. B., Gouliaev, G., et al (1993) Mortality in Danish psychiatric long-stay patients, 1972–1982. *Acta Psychiatrica Scandinavica*, **87**, 336–341.

McKeith, I., Fairbairn, A., Perry, R., et al (1992) Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *British Medical Journal*, **305**, 673–678.

Naftdowitz, D. F., Donovan, S. & Frances, A. (1995) The new polypharmacy in psychiatry: clinical practice and clinical research part company. *CNS Drugs*, **4**, 404–409.

Rakowski, W. & Mor, V. (1992) The association of physical activity with mortality among older adults in the longitudinal study of aging (1984–1988). *Journal of Gerontology*, **47**, M122–M129.

Saku, M., Tokudome, S., Ikeda, M., et al (1995) Mortality in psychiatric patients, with a specific focus on cancer mortality associated with schizophrenia. *International Journal of Epidemiology*, **24**, 366–372.

Stones, M. J., Dornan, B. & Kozma, A. (1989) The prediction of mortality in elderly institution residents. *Journal of Gerontology*, **44**, P72–P79.

Waddington, J. L. (1992) Mechanisms of neuroleptic-induced extrapyramidal side effects. In *Adverse Effects of Psychotropic Drugs* (eds J. M. Kane & J. A. Lieberman), pp. 246–265. New York: Guilford Press.

__ **(1993)** Schizophrenia: developmental neuroscience and pathobiology. *Lancet*, **341**, 531–536.

__ **(1995)** The clinical psychopharmacology of antipsychotic drugs in schizophrenia. In *Schizophrenia* (eds S. R. Hirsch & D. R. Weinberger), pp. 341–357. Oxford: Blackwell.

__ , **Youssef, H. A., Dolphin, C., et al (1987)** Cognitive dysfunction, negative symptoms and tardive dyskinesia in schizophrenia. *Archives of General Psychiatry*, **44**, 907–912.

__ , __ **& Kinsella, A. (1990)** Cognitive dysfunction in schizophrenia followed up over five years, and its longitudinal relationship to the emergence of tardive dyskinesia. *Psychological Medicine*, **20**, 835–842.

__ , __ **& __ (1995)** Sequential cross-sectional and 10-year prospective study of severe negative symptoms in relation to duration of initially untreated psychosis in chronic schizophrenia. *Psychological Medicine*, **25**, 849–857.

Weinberger, D. R. (1995) Schizophrenia: from neuropathology to neurodevelopment. *Lancet*, **346**, 552–557.

Working Group of the Royal College of Psychiatrists, Psychopharmacology Sub-Group (1997) *The Association Between Antipsychotic Drugs and Sudden Death.* Council Report CR57. London: Royal College of Psychiatrists.

World Health Organization (1978) *Mental Disorders: Glossary and Guide to their Classification in Accordance with the Ninth Revision of the International Classification of Diseases.* (ICD–9). Geneva: WHO.

World Health Organization Heads of Centres Collaborating in WHO Coordinated Studies on Biological Aspects of Mental Illness (1990) Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment. A consensus statement. *British Journal of Psychiatry*, **156**, 412.

Yoneyama, T., Hashimoto, K., Fukuda, H., et al (1996) Oral hygiene reduces respiratory infections in elderly bed-bound nursing home patients. *Archives of Gerontology and Geriatrics*, **22**, 11–19.