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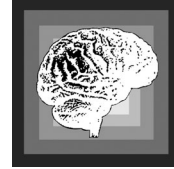
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The impact of mood stabilizers on bipolar disorder: the 1890s and 1990s compared

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This study comparing patterns of service utilization by bipolar patients in North-West Wales found a greater prevalence of service utilization in the 1990s compared with the 1890s. In the pre-lithium era, admissions for bipolar disorders occurred at a rate of 4 every 10 years; they now occur at a rate of 6.3 every 10 years. Where 100 years ago, there were 16 bipolar patients per million population resident per day in hospital, there are now 24 per million resident in acute service beds and more in non-acute beds. These data are incompatible with simple claims that mood stabilizing drugs 'work'. An alternative is that these agents have treatment effects, and further research is needed to match treatments to patients in order to optimize outcomes.

Keywords: *bipolar disorder; Britain; incidence; manic-depressive illness; prevalence; service utilization; 19th century; 20th century*

Introduction

Whether or not clinical trials demonstrate a treatment effect for drug X in condition A, there is also the question as to whether treatment is effective or even partially effective. If medical treatments are fully effective, the index condition should disappear, as general paralysis of the insane disappeared after the introduction of penicillin. When a condition completely disappears, clinical trials or other methods to evaluate treatment efficacy become

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redundant. When there is partial or debatable efficacy, as with the use of mood-stabilizers for bipolar disorders (manic-depressive illness), historical epidemiological studies, among others, can offer some answers as to whether current clinical practice is judicious or not.

There is a further problem when it comes to attempting to evaluate the efficacy of mood-stabilizers in a complex condition such as bipolar disorder, which requires indicators of efficacy other than a signal that a treatment has an acute effect on a condition. An effect on depression does not mean that this treatment will be useful for manic-depressive illness – it might in fact make the overall condition worse. This, allied to the difficulties in undertaking controlled trials in bipolar disorders, means that systematic comparisons between historical and modern samples of patients have a particular importance in this treatment area, as controlled trials are less likely to provide a clear signal of therapeutic efficacy.

In terms of undertaking historical epidemiological research, service utilization for mental health disorders in North Wales has mirrored the general United Kingdom pattern of service utilizations through the nineteenth and twentieth centuries. Thus from the year of its opening in 1848 through to the introduction of chlorpromazine in the 1950s, the inpatient population in the North Wales Hospital rose exactly in parallel with the general rise in the UK asylum population. The most common admissions for severe functional mental illness were for schizophrenia and related psychoses or for severe unipolar and bipolar affective disorders.

In addition, the services in North-West Wales offer opportunities to exploit the capabilities of historical epidemiology to shed light on current approaches to the management of a range of conditions such as bipolar disorder for a number of specific reasons. First, compared with elsewhere, NW Wales has not seen a general increase in its population over this period. A census of the population broken down by age in 1891 showed that there were 232,000 people, and 241,000 from the same area in 1991. For the critical age groups between 15 and 55 the respective populations were 117,000 and 119,000 people (Healy, Savage, Michael, Harris, *et al.*, 2001).

Second, elsewhere in the UK, in addition to population increases, there have been population shifts over the past century, so that it becomes uncertain whether it is possible to draw a comparison between admissions to a rural asylum 100 years ago with admissions to an urban district general hospital unit now, but these shifts did not happen in NW Wales, so admissions over a 100-year period can be more readily compared.

Third, whereas elsewhere a variety of geographical and financial factors make it difficult to determine how representative those who access a service are of the whole population of the mentally ill, geography and finance have conspired in NW Wales to ensure that patients effectively had only one point of access to services in both the 1890s and 1990s. Any featured map of NW Wales makes it clear that the areas being served are locked in by the Irish Sea on one side and

the Snowdonian mountain range on the other. It was simply not possible to access easily any other service within a hundred miles in the 1890s, other than the asylum at Denbigh. Similar constraints applied in the 1990s with the extra proviso that National Health Service (NHS) requirements meant that any patients from NW Wales accessing a service elsewhere in the country were liable to be returned for treatment. In the 1890s NW Wales was one of the poorest areas of the country and it remains so today. There was an essentially negligible amount of private practice in the 1890s, and this remains the case in the 1990s.

Accordingly we set up a study to compare rates of admission from NW Wales to the North Wales asylum through the 1890s compared with admissions to the corresponding district general hospital unit today (Healy *et al.*, 2001). In brief, there was evidence: that across diagnostic boundaries, three times more people are detained now compared with the 1890s; that fifteen times more patients are admitted; and that patients from a range of diagnostic groups who would not have been admitted in the 1890s are admitted now. But what of patients with bipolar disorders?

Methods

In North Wales, there are comprehensive and clear records from the Denbigh Asylum, from its opening in 1848 through to its closure. The historical background to the asylum, the populations involved in this study, and the methods of data entry are laid out elsewhere (Healy *et al.*, 2001).

Admissions from NW Wales now are to a 60-bed district general hospital unit, the Hergest Unit. At the time of this project, this unit had seven adult mental illness consultants delivering a sectorized service. It was a high-morale service with few staff vacancies, a low bed occupancy rate (80%) compared with UK standards, and well established and well functioning mental health teams.

Diagnosis

Records from the 1890s and the 1990s from what are now termed different sectors were given to the sector consultant for diagnosis. This means that whatever biases an individual consultant may have applied to their 1990s sample will have been applied also to the 1890s sample.

The 1890s records contained the details that had led to certification as well as relatively clear descriptions of the mental and physical state of the patient at the time of admission, followed by detailed notes of subsequent hospital stays. In the case of 1890s patients with admissions prior to 1890 or subsequent to 1900, we were able to track down all earlier records to 1875 and all further admissions through to 1925. Clinicians making a retrospective diagnosis had all prior and subsequent records available to them and accordingly diagnostic judgements were made on the overall career of the patient rather than simply on the details of the presenting mental state.

The 1990s comparative sample consisted of all admissions to a 60-bed DGH psychiatric unit, between 1 April 1996 and 31 March 1997 (the 1996 sample) and between 1 March 1999 and 28 February 2000 (the 1999 sample). Admissions could be through walk-ins, referral from the local DGH, referrals from general practitioners, from the police, from mental health teams or through the sector consultant. Admissions consisted of general adult mental illness cases; childhood, adolescent, learning disabilities and dementia patients went elsewhere. This service had additional support bed hostels, a generous provision of EMI assessment, respite and long-stay beds and separate services for childhood disorders and learning disabilities.

The traditional methodological caveat about diagnosis in historical epidemiology concerns the validity of diagnoses made on a deceased sample. This might have some validity for a diagnosis taken on a cross-sectional mental state, but these diagnoses were based on the longitudinal history, and the 1890s patients were categorized in broad diagnostic groups: psychosis, affective disorder (bipolar or recurrent unipolar), personality disorder, and delirium or dementia (Healy, Harris, Michael, Cattell, *et al.*, 2005). A more serious methodological concern may well lie with the contemporary sample. Recent research suggests that up to 10% of patients going through a DGH unit today will have catatonic features. Catatonia, which has been obituarized extensively, in fact appears not to have gone away, but apparently modern psychiatrists simply do not see quite bizarre and striking features of the mental states of their patients under their noses (Healy *et al.*, 2005). Finally, the diagnosis of bipolar disorder in both the 1890s and 1990s sample refers to bipolar 1 exclusively – that is, admissions for treatment rather than episodes of illness are counted.

Analysis of data

We first compared the per annum admission rate in the 1890s and 1990s samples. We defined admission prevalence as the number of individuals admitted in a one-year period. Second, we examined the hospitalized incidence rates for bipolar disorders. Third we calculated the length of stay of patients and the numbers of prior admissions. Finally, we have sought figures for both mean length of stay and overall usage of service beds by disease cohorts.

As noted above, there was a similar age distribution between the populations in the 1890s and 1990s across the 15–65 age groups. Therefore we have only supplied the numerators for the bipolar group.

Based on clinical outcome terms used in the 1890s sample, we developed operational criteria to categorize the course of the illness. In both 1890s and 1990s samples, there were four possible outcomes for patients.

- (1) Discharged 'recovered'; these patients had to have less than 3 admissions in the 3 years prior to the index admission, to be discharged home with a

clinical diagnosis of recovery recorded in their notes and no admission during the year after discharge.

- (2) Discharged 'relieved', in which case the clinical notes recorded that the acute symptoms had passed but the patient was not back to normal and was discharged to a hostel (1990s) or to the workhouse or lodgings (1890s). Such patients characteristically had 3 or more prior admissions in the 3-year period before the index admission and/or an admission in the year after discharge.
- (3) Discharged 'not improved'.
- (4) Died in care.

Using these operational definitions, some patients designated as recovered in the 1890s by their clinicians were re-designated as relieved on the basis of a further admission within a year of their apparent recovery.

In order to establish the number of bed-days occupied in the 1890s, we accessed all prior and subsequent records of this cohort of patients and summed their lengths of stay. For the 1990s cohort, we accessed all prior records and similarly summed prior admissions. In addition to lengths of hospital stay, we also recorded inter-illness intervals between all illness episodes from the point of first admission for all patients from both the 1890s and the 1990s.

Results

The 1890s sample

A key issue here is that the terms mania and melancholia in the English-speaking world up to 90 years ago referred to overactive and underactive insanities rather than to what we would now regard as bipolar disorders. Patients who would now be diagnosed with schizophrenia or even agitated depression were diagnosed then with mania (Berrios, 1981).

In the course of the 1890s, 593 individuals from NW Wales had 679 admissions to the asylum, of which 278 were women and 315 were men. Of these 593 patients, 303 were diagnosed then as having mania and 154 as having melancholia on either their only admission or their first admission in this period. Of these 1890s diagnoses of mania, modern consultant psychiatrists diagnosed 9% as having bipolar illness. Of the patients with a diagnosis of melancholia, 7% were diagnosed as bipolar patients.

Using contemporary diagnostic criteria, there were in all 37 bipolar patients, 22 females and 15 males, who had between them 59 admissions between 1 Jan. 1890 and 31 Dec. 1899. When further admissions between 1875 and 1924 were included, this cohort of patients had 161 admissions in all during their psychiatric careers. Bipolar patients from this cohort therefore had on average 6 admissions per annum during the 1890s. This is a

service utilization prevalence of 36 admissions per million per annum or 0.0036% per annum. Of these 37 individuals, 18 had a previous episode of illness that did not lead to admission, making at least 179 episodes in all or a mean of 4.8 affective episodes per person. There was a mean of 4.4 hospital admissions per person (median 3.0).

In this sample, 22 of the 37 patients were admitted for the first time during the 1890s, 12 women and 10 men. The incidence of first admissions varied from 1 to 5 per year with a mean of 2.2 per year, or 9 per million per year, an incidence rate of 0.0009%. Half of these 22 patients had had a previous attack not treated in the asylum.

The mean age at first hospitalization for all 37 patients was 32.2 years (median 29), 32.9 years for females and 31.1 years for males. The average length of a stay in hospital was 621 days (median 239). The length of the average illness episode was 338 days (median 184).

The 22 women in the sample had 106 admissions, with an average length of 310 days per admission (median 180). Excluding final episodes resulting in death, this becomes 273 days (median 170). The 15 men had 55 episodes, with an average length of stay of 392 days with a median value of 221 days for all episodes. Excluding death in care episodes, the figures were 232 days (median 214). This combination and number of episodes gave rise to a mean inter-illness interval of 1393 days for the whole group (median 678), a median length of stay of 239 days and median inter-illness interval of 678 days. This results in patients having on average 4 illness episodes per 10 years, which is exactly the traditional figure cited for illness episode frequency before lithium.

However, men and women differ. For women the mean inter-illness interval is 1167 days (median 479), while for men the figures are 1866 days (median 1482). This means women in 1896 had an average of 5 episodes in 10.6 years with men having 2 episodes in 9.3 years. Women had on average 4.8 admissions with men having 3.7 admissions. Of the 106 female admissions, 72% were for manic episodes, 15% for depression and the remainder were mixed. Of the 55 male admissions, 75% were manic, 6% were for depression and the remainder were mixed.

Of the 22 first admissions, a hereditary component was noted in the clinical records in the case of 11 patients (50%) – 4 parents, 3 siblings, 4 uncles, aunts or cousins. The commonest triggering cause cited for women on first admission was puerperal (4), or death or illness of a relative (5), with domestic difficulties in 2 instances. For men, hereditary (2), previous (3) and physical factors (3) were suggested as causes.

The 1990s sample

In 1996, there were 737 hospital admissions for mental illness from 542 individuals. Of these, 45 individuals were admitted with a bipolar diagnosis. In 1999 there were 638 admissions from 476 individuals. Of these, 37 patients were admitted with a bipolar diagnosis.

Of these 82 bipolar patients in total, we excluded 2 (one from each year), who on case review did not meet criteria for bipolar illness. We also excluded an 80-year-old lady whose illness had begun aged 78. Nine patients, 6 from 1996 and 3 from 1999 were from out of area or had left the area and are not counted further. Of five patients who died, the records of two are currently not available and these are not included in this analysis. Of the remaining 70 patients, 12 presented in both years, giving 58 individuals in total, or 29 per annum on average; subtracting the two untraceable records leaves 56 patients considered further. These 56 individuals had a total of 103 admissions during the two-year period. Counting out of area admissions, there were 110 admissions, 55 per annum on average. This is an annual service utilization rate of 220 per million (0.022%)

These 56 patients had a mean age of onset of 30.9 years. There were 37 female patients with a mean onset of 31.8 years and 19 males with a mean onset of 28.9 years. The 1990s cohort had had 596 admissions by the end of 2000, a current career mean of 10.6 admissions per patient, and a median value of 7.5 admissions per patient.

The mean length of stay per person was 39.6 days (median 36). The average total length of stay per patient over their career to the year 2000 was 438 days. The total length of stay of an annual cohort in the 1990s was 7830 days, compared with 3192 days for an annual cohort in the 1890s. The average inter-illness interval in the 1990s was a mean of 872 days (median 550). This median length of stay and median inter-illness interval gives rise to a rate of 6.3 episodes per 10 years

Again women and men differed, with women having a mean of 12.6 admissions (median 8) and men a mean of 8.4 admissions (median 6). Women had a mean length of stay of 38 days (median 36), and a mean inter-illness interval of 689 days (median 458). For men, the mean length of stay was 42 days (median 39) and a mean inter-illness interval of 1229 days (median 734). These figures give rise to admission rates of 7.4 in 10 years for women and 4.7 in 10 years for men.

Comparative figures

Twelve of the patients diagnosed with bipolar disorder in 1996 were detained under the 1983 Mental Health Act. Ten of the patients diagnosed with bipolar disorder were detained in 1999. This gives an average of 11 detentions per annum, double the rate of detention found in the 1890s.

Of the 1996 patients, 5 had had no previous admissions. There were two new bipolar patients in 1999 making 7 in total for both years, an average of 3.5 per year. While there is no clear difference in the annual incidence rate between the 1890s and the 1990s in this sample, there would appear to be at least double the number of patients in the system now than then, pointing to an increased incidence as well as prevalence of service utilization for bipolar disorders.

TABLE 1. *Bipolar patients compared in two periods*

	1890–99	1996 & 1999
Total no. patients	37	58
Mean no. patients per annum	3.7	29
Total no. admissions	161	591
Females	60%	66%
Incidence of service utilization	0.0009%	0.0014%
Prevalence of service utilization	0.0036%	0.022%
Mean age of onset	32.2 years	31 years
Median hospitalization stay	239 days	36 days
Median inter-hospitalization interval	678 days	540 days
Median no. hospitalizations	4 in 10 years	6.3 in 10 years
Median no. bipolar residents/day	4	6

Comparing figures from the 1890s with the 1990s, there is a greater likelihood of having a bipolar patient in a service bed now than before. In the 1890s, an average of 6 admissions per annum giving rise to stays with a median length of 239 days leads to a median annual figure of 1434 bed-days or 3.9 patients in a bed every day of the year (16 patients per million). In the late 1990s, the equivalent figures were 56 admissions, with a median stay of 39 days, giving rise to 2184 bed-days or 5.98 patients in a bed every day of the year (24 patients per million); see Table 1.

In the case of the 1890s bipolar patients, 13 of 161 admissions ultimately led to chronicity/death in the asylum (8% of admissions). The other options were to be discharged recovered, relieved or unchanged. As outlined, these concepts were operationalized so that readmission within 3 years would lead to a discharge status of relieved rather than recovered, as would discharge to the workhouse or elsewhere rather than to home (Healy *et al.*, 2005). Of 161 admissions in the 1890s, 131 led to discharges as recovered (81%). Thirteen of the patients were discharged as relieved (8%).

In the case of 1990s bipolar patients, using these operational criteria, 17% were discharged recovered, while 77% were relieved and by 2003, 6% had either died or become chronic inpatients. These data on bed occupancy for the 1990s cohort do not include hostel or other bed provision. If those are

taken into account, the figures for service utilization in the 1990s sample will be higher than has been estimated here.

Discussion

Bipolar disorders are at present intensely fashionable. The mainstay of their treatment is a group of psychotropic drugs, of which lithium, valproate and carbamazepine are the best known. These drugs have been distinguished as a separate class of agent and termed mood-stabilizers only since the 1990s (Harris, Chandran, Chakraborty and Healy, 2003). This name suggests that the drugs in question have been shown to reduce the frequency of bipolar episodes, when in fact this has not been shown and is perhaps practicably impossible to show using randomized controlled trial methods. In the absence of clear evidence of efficacy, there is a need for other data that might provide indicators of efficacy. These data on service utilization from the periods 1890–99 and 1996 and 1999 offer some indications of treatment success and problems.

The historical sample drawn from NW Wales shows reasonable overlap with figures on manic-depressive illness from Kraepelin (1896), who reported that 15% of his admissions were for bipolar disorder and that two-thirds of the sample were female. In this sample, a lower proportion of the bipolar group were female (60%), and bipolar disorders only accounted for 9% of admissions, but these differences may stem primarily from the fact that admissions to Munich were highly selected.

The NW Wales figures make it clear that we now manage acute episodes of bipolar disorder relatively well; there are shorter lengths of stay in acute inpatient settings in the year 2000 than there were in 1900. This management, however, does not appear to translate into a greater amount of time recovered or indeed into less service utilization in 2000 than in 1900. Despite extensive prescribing of mood stabilizers, especially lithium, patients in 2000 have 6.3 admissions per 10 years compared to 4 admissions per 10 years from the pre-lithium period.

A number of factors may play a part in producing outcomes like this. First, while there may be a question as to how many of these patients were taking their medication, these findings for bipolar disorder are comparable to findings for the other major psychiatric syndromes (Healy *et al.*, 2005). Second, the increased service utilization for psychiatric syndromes in general overlap with increases in service utilization in the rest of medicine (Healy *et al.*, 2001). There would therefore seem to be a set of general health factors in addition to any specific bipolar disorder factors at play to produce at least part of the change seen here (Healy *et al.*, 2001).

Third, there may have been a shift in the nature of patients diagnosed as bipolar. Lithium and other 'mood-stabilizers' have almost certainly had an impact on diagnostic practices and thereby on service utilization patterns.

Patients who would once have been thought as having a personality disorder or other behavioural psychosyndromes are now diagnosed in some instances as having a bipolar disorder on the basis of responsiveness to lithium or an anticonvulsant. When tracking back through the records of our 1990s sample, it became clear that there are a number of patients who began their psychiatric career with a manic-depressive diagnosis, whose diagnosis then shifts to hysterical or borderline personality disorder, but who on discontinuation of lithium have a much greater frequency of admissions. Does this response to lithium indicate that the correct diagnosis actually was bipolar disorder?

The early history of lithium points to an effect of treatment in changing diagnostic practice. While Cade's original patients made bipolar disorder appear like a lithium deficiency disorder, the seminal work of Angst and colleagues points to other possibilities. In one of the most comprehensive service utilization studies of lithium prophylaxis (Angst, Weiss, Grof, Bastrup and Schou, 1970), the cohort of patients studied had an average of more than 1 admission per annum prior to lithium treatment, a rate even higher than reported in our 1990s sample. This rate was reduced to 1 admission per 2 years with lithium treatment. Our 1890s figures suggest that such rates of service utilization are quite atypical of classic manic-depressive disease, raising the possibility that the key clinical sample in the prophylaxis debate contained 'borderline' or other patients not typical of the classic manic-depressive profile. At the very least there was a significant selection bias in these classic lithium studies – one that was conceded by the authors themselves.

Fourth, there may be important ambiguities in the relationship between illness episodes and hospitalization. Some of the strongest recent data on lithium prophylaxis in manic-depressive illness comes from the large relatively unselected sample reported by Tondo, Baldessarini and Floris (2001). This sample overlaps both the 1890s and 1990s samples reported here in terms of sex ratios and age of onset. The study had a mean rate of admission pre-lithium of once every three years – which approximates the rate of admission from our 1890s sample. In this sample, lithium reduced the rate of hospitalization to less than once in every ten years. These are the kind of changes that might be expected of a prophylactic treatment. Given that these data do not arise from randomized trials, it is possible that subtle selection factors or concomitant adjuvant therapeutic inputs may have contributed to the benefits. Whatever the origin of the benefits, there is a dramatic difference between this mood-stabilized sample and our 1990s cohort in terms of hospital admissions.

However, the frequency of episodes in the sample reported by Tondo and colleagues remains high, at 1.8 per annum. While lithium reduces this frequency, the treated frequency remains at 8 episodes per 10 years. Furthermore, a striking feature of the dataset assembled by Tondo and colleagues is that these illness episodes last over 100 days. This suggests that

even in the modern period the true length of manic-depressive episodes is far closer to those experienced 100 years ago than data on modern service utilization might suggest. If in a proportion of modern patients the data from consecutive admissions in fact reflect a single illness episode rather than multiple discrete episodes, this would help reconcile the two datasets.

Of note in this regard is the fact that compared with the NW Wales 1890s data set, the 1990s sample showed a far greater proportion of admissions for depression. Approximately 50% of current admissions are for depression. This may stem from a lowered threshold for admissions for non-delusional depression to modern clinical facilities (Healy *et al.*, 2001). Alternatively, modern pharmacotherapies may produce a range of dysthymic states that against a background of a diagnosed manic-depressive illness will trigger admissions, owing to the perceived risk of suicide from the underlying bipolar condition. It is not impossible, however, that repeated hospitalizations or repeated medication changes (pharmacological life events) may add appreciably to the risk of suicide.

Fifth, many modern treatments especially those used in the acute phase of treatment may produce complicating effects in the longer run. The proponents of the merits of mood stabilizers in bipolar disorders argue that many agents such as tricyclic antidepressants may lead to increased rates of service utilization by causing bipolar patients to cycle more rapidly (Ghaemi, Sachs, Chiou, Pandurangi and Goodwin, 1999). These figures are potentially consistent with just such a possibility.

Quite aside from inducing rapid cycling, it is becoming clearer that there can be significant physical dependence on both antipsychotics and antidepressants (Healy & Tranter, 1999), and that deliberate or inadvertent discontinuation of treatment will lead to episodes likely to require hospitalization. In part, this arises from the fact that while these agents may break up an affective or psychotic syndrome, they do not correct the underlying defect in these syndromes. Administration of standard antidepressants and antipsychotics is therefore a brain stressor in its own right with potentially complex outcomes. Whether this is also likely to be true of mood stabilizers remains to be seen.

In summary, this study suggests that historical epidemiology can shed significant light on the effect treatments have when given in real treatment settings rather than in controlled trials. Such research becomes even more important when a particular treatment is not readily open to evaluation using controlled trial methods. Using such an approach in the case of bipolar disorders indicates that there is no room for complacency in either the conceptual domain or in the domain of clinical practice, in that modern treatments appear to offer few benefits compared with treatment 100 years ago.

The relatively small numbers used in this study did not permit answers to the question of whether there is a difference in the incidence of service utilization by bipolar patients in previous periods compared with now. The rates of incidence for this disorder were comparatively low in the historical

period, suggesting that in order to answer questions on incidence, up to 40 years' worth of data from a catchment area the size of NW Wales, or 10 years' worth of data from a catchment area of a million people, would need to be compared with up to a decade of data from current service utilization. A study to capture these data in NW Wales is underway.

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