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Who is prescribed valproate and how carefully is this treatment reviewed in UK mental health services? Data from a clinical audit

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Abstract

Background: The licensed indications for valproate are narrow, yet this medication is commonly prescribed in mental health services.

Objectives: To explore the target symptoms/behaviours for which valproate is prescribed and how well the efficacy and tolerability of this treatment are monitored in routine clinical practice.

Design: An audit-based quality improvement (QI) programme in UK mental health services.

Methods: Information on valproate prescribing was collected from clinical records using a bespoke data collection tool.

Results: Sixty-four NHS mental health Trusts/healthcare organisations submitted data on valproate treatment for 5320 patients. Valproate was clearly prescribed for a licensed indication in 1995 (38%) patients, off-label in 1987 (37%) while the indication was uncertain/not available in 1338 (25%). Of the 919 patients started on valproate treatment within the past year, between a half and two-thirds had each of the relevant baseline physical health checks documented. In 539 (59%) of these patients, valproate was prescribed for an unlicensed indication; the prescription was recognised as off-label in 363 (67%), 20 (6%) of whom were documented as having had this explained to them. Of 631 patients prescribed valproate for between 3 months and a year, early on-treatment assessments of response and side effects were documented in 441 (70%) and 332 (53%), respectively. Of 4401 patients treated for more than a year, annual on-treatment reviews of clinical response and side effects were documented in 2771 (63%) and 2140 (49%), respectively.

Conclusion: Our data suggest the majority of prescriptions for valproate in mental health services are not for a licensed indication. Furthermore, patients rarely receive an explanation that their valproate prescription is off-label, perhaps partly because the licensed indications are not widely understood by prescribers. Given the very limited evidence for efficacy for the off-label uses of valproate, failure to routinely conduct early on-treatment and annual reviews of the benefits and side effects of this medication may result in patients remaining on ineffective and poorly tolerated treatment by default.

Keywords: bipolar disorder, off-label, personality disorder, schizophrenia, treatment monitoring, valproate

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Introduction

The National Institute for Health and Care Excellence guidelines for bipolar disorder[1] support the use of valproate as an adjunctive treatment for episodes of hypomania/mania and bipolar depression and for relapse prevention in bipolar disorder

although it is not considered to be a first-line option for any of these indications. These evidence-based recommendations are broadly consistent with those made by the British Association for Psychopharmacology (BAP) in their guideline for the treatment of bipolar disorder[2] and the licensed indications for valproate in its semisodium formulation.[3]

Despite the narrow, licensed indications for valproate in psychiatry and the limited recommendations supporting such use in clinical guidelines, this medication is commonly prescribed in UK mental health services, suggesting that it often used off-label. There are data to support this assumption. For example, a clinical audit conducted in the context of an audit-based quality improvement (QI) programme by the Prescribing Observatory for Mental Health (POMH), focusing on the quality of prescribing practice with long-acting injectable (LAI) antipsychotic medication, found that one in ten of 4962 patients on such medication and with a sole psychiatric diagnosis of schizophrenia were co-prescribed valproate.[4] In a further POMH QI programme addressing the use of clozapine, the proportion co-prescribed valproate was higher, at almost one in six of the 7034 patients on clozapine in the national clinical audit sample.[5] With respect to prescribing for personality disorder, an audit conducted as part of another POMH QI programme found that one in five of 786 patients with emotionally unstable personality disorder as their sole psychiatric diagnosis was prescribed a mood stabiliser, predominantly valproate.[6]

In 2021, a QI programme focusing on the use of valproate was initiated by POMH. This afforded the opportunity to explore the target symptoms/behaviours for which valproate is prescribed in UK mental health services and how well the efficacy and tolerability of this treatment are monitored in routine clinical practice.

Method

For the last 16 years, POMH has been running QI programmes on prescribing practice for UK mental health services.[7] In 2020, a baseline audit was conducted as part of a programme addressing the use of valproate in psychiatric practice. All 66 POMH member Trusts/healthcare organisations were invited to take part. The clinical practice standards for audit were derived by the authors from the NICE guideline for the assessment and management of bipolar disorder,[1] the BAP guideline for bipolar disorder[2] and the report by the Royal College of Psychiatrists on the use of licensed medicines for unlicensed applications in psychiatric practice[8] and agreed with expert clinical advisors and clinicians from member Trusts as representing best practice. The practice standards were as follows:

1. A clinician's reasons for initiating valproate treatment (i.e. target symptoms or behaviour) should be documented in the clinical records.
2. If valproate is being prescribed off-label, it should be documented that this has been explained to the patient.
3. Prior to initiating treatment with valproate, the following should be documented in the clinical records: weight and BMI, the results of liver function tests (LFTs) and a full blood count (FBC).
4. Review within the first 3 months of valproate treatment should include assessment of the response of the target symptoms/behaviour and screening for common side effects of the medication.
5. Patients prescribed continuing valproate treatment should have an annual review of the risk-benefit balance. This should include assessment of therapeutic benefit, adverse effects and medication adherence.

Trusts were asked to submit data on prescribing practice for a sample of patients who were prescribed valproate, under the care of adult mental health services. These data included age, sex, ethnicity, psychiatric diagnosis, the nature of the clinical service providing care, the clinical reasons for prescribing valproate, the dose and duration of valproate treatment, and other psychotropic medications prescribed with valproate. Where valproate had been prescribed for less than a year, data were collected on pre-treatment physical health checks (conducted within the 3 months before the start of valproate treatment), documented explanations of off-label use and early on-treatment review of efficacy and side effects. Where valproate had been prescribed for more than a year, data were collected on annual reviews of efficacy and side effects.

Valproate is a known major human teratogen and its use is contraindicated in women of child-bearing potential unless the conditions of 'prevent', the pregnancy prevention programme, are fulfilled.[3,9,10]

Information was therefore also collected[11] on the implementation of 'prevent', but this is outside the scope of this article and so is not reported here. Relevant data from a previous POMH audit have been published elsewhere.[12]

Clinicians and clinical audit staff collected data using the same bespoke audit tool. The data collection period was September and October 2020. All data were obtained from the clinical records with the exception of the clinical reason for valproate treatment; clinical teams could be asked directly for this information if it was not available in the clinical records. All data were pseudonymous within the Trusts and submitted anonymously to POMH, using Formic software.[13] Ethical approval is not required for such an audit-based QI initiative.[14] The data were analysed using SPSS.[15]

Results

Sixty-four NHS Trusts/healthcare organisations submitted data related to the use of valproate in 5320 patients under the care of adult mental health services. Valproate had been prescribed for less than a year in 919 (17%) cases and more than a year in 4401 (83%).

The demographic and clinical characteristics of the patient sample are shown in Table 1. Three-fifths of the sample were male ($n=3210$; 60%) and over half ($n=2719$; 51%) were between 36 and 55 years of age. Almost nine out of ten ($n=4625$; 87%) patients had a diagnosis of either schizophrenia or bipolar disorder and a quarter of the sample ($n=1371$; 26%) had two or more psychiatric diagnoses. The vast majority of patients ($n=4718$; 89%) were under the care of adult psychiatric teams, of whom over three-quarters (3704; 79%) were under the care of community mental health teams.

Clinical reasons for prescribing valproate

The reason for prescribing valproate was documented in the clinical records for 3808 (72%) patients and obtained from the clinical team for a further 732 (14%), leaving 780 (15%) patients for whom the reason for prescribing valproate was not available. The first practice standard was therefore not met in 1512 (28%) cases.

In the 4540 (85%) patients for whom the clinical reason for prescribing valproate was available, this was clearly a licensed indication in 1995 (44%) cases, most commonly to prevent manic/hypomanic relapse in bipolar disorder ($n=1294$; 65%), to treat an acute episode of mania ($n=732$; 37%) or to treat epilepsy/seizures ($n=321$; 16%). The clinical reason for prescribing valproate was clearly off-label in 1987 (44%) cases, most commonly referring to the management of mood symptoms or affective instability in patients with diagnoses other than bipolar disorder ($n=1779$; 90%). In the remainder of cases ($n=558$; 12%), there was insufficient information available to determine whether valproate was prescribed within its licensed indications or not, for example, for the prevention of clozapine-induced seizures ($n=148$; 27%).

To investigate the clinical reasons for prescribing valproate for individual psychiatric diagnoses, the data were removed on patients with more than one such diagnosis documented in their clinical records. This resulted in three subgroups, reflecting the most common sole psychiatric diagnoses in the audit sample: 1756 (33%) patients with a sole diagnosis of schizophrenia spectrum disorder, 1667 (31%) with a sole diagnosis of bipolar disorder and 163 (3%) with a sole diagnosis of personality disorder. For each of these three diagnostic subgroups, the most common clinical reasons for prescribing valproate are shown in Table 2 and other psychotropic medications co-prescribed with valproate are shown in Table 3.

Documentation that the use of valproate off-label had been explained to the patient

In the subsample of 919 patients who had been prescribed valproate for less than a year, the prescription was clearly for a licensed indication in 380 (41%) cases. Of the remaining 539, the prescription was identified as being for an off-label indication in 363 cases. In 20 (6%) of these cases, practice standard 2 was met in that there was documentation in the clinical records to indicate that the off-label nature of the valproate prescription had been explained to the patient.

Physical health checks in the 3 months prior to starting valproate

Of the 919 patients prescribed valproate for less than a year, the following tests/measures were documented as having been conducted prior to the initiation of valproate: an FBC in 618 (67%) cases, LFTs in 607 (66%), blood pressure in 603

Table 1. Demographic and clinical characteristics of the total, national, clinical audit sample of patients prescribed valproate.

			***n* = 5320** ***n* (%)**
Sex	Male		3210 (60)
	Female		2110 (40)
Ethnicity	White/White British		4022 (76)
	Black/Black British		379 (7)
	Asian/Asian British		344 (6)
	Mixed or other		282 (5)
	Not collected/stated		293 (6)
Age in years	Median age (range)		49 years (17–90)
	Age bands	17–25	238 (4)
		26–35	758 (14)
		36–45	1145 (22)
		46–55	1574 (30)
		56–65	1204 (23)
		Over 65	401 (8)
ICD-10 diagnosis	F00-F09: Organic disorder		125 (2)
	F10-19: Disorders due to psychoactive substance use		572 (11)
	F20-29: Schizophrenia spectrum disorder		2442 (46)
	F30-39: Mood disorder	Bipolar disorder	2183 (41)
		Other affective disorder	346 (7)
	F40-48: Neurotic, stress-related and somatoform disorders		252 (5)
	F50-59: Behavioural syndromes associated with physiological disturbances and physical factors		14 (<1)
	F60-69: Personality disorder	Paranoid	26 (<1)
		Dissocial	111 (2)
		Emotionally unstable	457 (9)
		Other personality disorder	137 (3)
	F70-79: Intellectual disability		176 (3)
	F80-89: Disorder of psychological development		108 (2)
	F90-98: Behavioural and emotional disorders with onset usually occurring in childhood and adolescence		75 (1)

(Cotinued)

Table 1. (Cotinued)

			***n* = 5320** ***n* (%)**
	F99: Unspecified disorder		10 (<1)
Clinical service providing care	General adult	Adult acute ward	665 (12)
		Psychiatric intensive care ward	116 (2)
		Inpatient rehabilitation ward	233 (4)
		Community mental health team	3704 (70)
	Forensic services	Forensic ward	478 (9)
		Prison psychiatric team	18 (<1)
		Community mental health team	62 (1)

Table 2. Daily valproate dose and the most common clinical reasons for prescribing in the three sub-groups of patients with a single psychiatric diagnosis.

	Patients in the national audit sample with a single psychiatric diagnosis					
	Schizophrenia spectrum disorder		**Bipolar disorder**		**Personality disorder**	
	n = 1756		**n = 1667**		**n = 163**	
Daily valproate dose: median (interquartile range)	1200 (800–1800)		1000 (800–1500)		1000 (750–1500)	
Most common clinical reasons for prescribing valproate (*n*, %)	To treat mood/ affective symptoms	1090 (62%)	To prevent manic/ hypomanic relapse	919 (55%)	To treat emotional instability	88 (54%)
	Adjunctive therapy for refractory symptoms	170 (10%)	To prevent depressive relapse	476 (29%)	To reduce impulsivity	27 (17%)
	Prevention of clozapine-related seizures	112 (6%)	To treat an acute episode of mania/ hypomania	430 (26%)	To treat epilepsy/ seizures	24 (15%)
	To treat persistent aggression/hostile behaviour	103 (6%)	To treat an acute episode of bipolar depression	160 (10%)	To reduce persistent aggressive/hostile behaviour	20 (12%)
	To treat epilepsy/ seizures	102 (6%)	To treat emotional instability	131 (8%)	To reduce deliberate self-harming behaviour	18 (11%)
	Unclear	280 (16%)		202 (12%)		36 (22%)

Table 3. Psychotropic medicines prescribed with valproate in the three sub-groups of patients with a single psychiatric diagnosis.

	Patients in the national audit sample with a single psychiatric diagnosis					
	Schizophrenia spectrum disorder		**Bipolar disorder**		**Personality disorder**	
	***n* = 1756**		***n* = 1667**		***n* = 163**	
	***n* (%)**		***n* (%)**		***n* (%)**	
Any antipsychotic medication	**1697 (97)**		**1272 (76)**		**112 (69)**	
Most commonly prescribed antipsychotic medication[a]	Clozapine	565 (32)	Quetiapine	370 (22)	Quetiapine	33 (20)
	Olanzapine	327 (19)	Olanzapine	324 (19)	Clozapine	20 (12)
	LAI zuclopenthixol	183 (10)	Aripiprazole	197 (12)	Olanzapine	19 (12)
	Aripiprazole	141 (8)	Risperidone	107 (9)	Aripiprazole	18 (11)
	Amisulpride	120 (7)	LAI zuclopenthixol	83 (5)	Chlorpromazine/ risperidone/haloperidol	7 (4)
Any antidepressant medication	**417 (24)**		**504 (30)**		**118 (72)**	
Most commonly prescribed antidepressant medication	Sertraline	137 (8)	Sertraline	140 (8)	Sertraline	32 (20)
	Mirtazapine	71 (4)	Mirtazapine	104 (6)	Mirtazapine	30 (18)
	Venlafaxine	64 (4)	Venlafaxine	86 (5)	Venlafaxine	29 (18)
	Fluoxetine	56 (3)	Fluoxetine	61 (4)	Duloxetine	10 (6)
	Citalopram	34 (2)	Citalopram	46 (3)	Amitriptyline	8 (5)
A benzodiazepine	**393 (22)**		**289 (17)**		**40 (25)**	
Lithium	**86 (5)**		**237 (14)**		**4 (2)**	
Lamotrigine	**35 (2)**		**123 (7)**		**7 (4)**	
Pregabalin	**37 (2)**		**63 (4)**		**20 (12)**	
Gabapentin	**10 (1)**		**30 (2)**		**5 (3)**	
Valproate as monotherapy	28 (2)		154 (9)		12 (7)	
Valproate plus one of the medications listed above	709 (40)		675 (40)		37 (23)	
Valproate plus two of the medications listed above	658 (37)		552 (33)		57 (35)	
Valproate plus three or more of the additional medications listed above	361 (21)		286 (17)		57 (35)	

LAI, long-acting injectable.
[a]All are oral formulations unless otherwise specified.
The bold text indicates totals for different medication classes. The text in the rows below are individual medications within the class shown above in bold; essentially subsets of the bold rows.

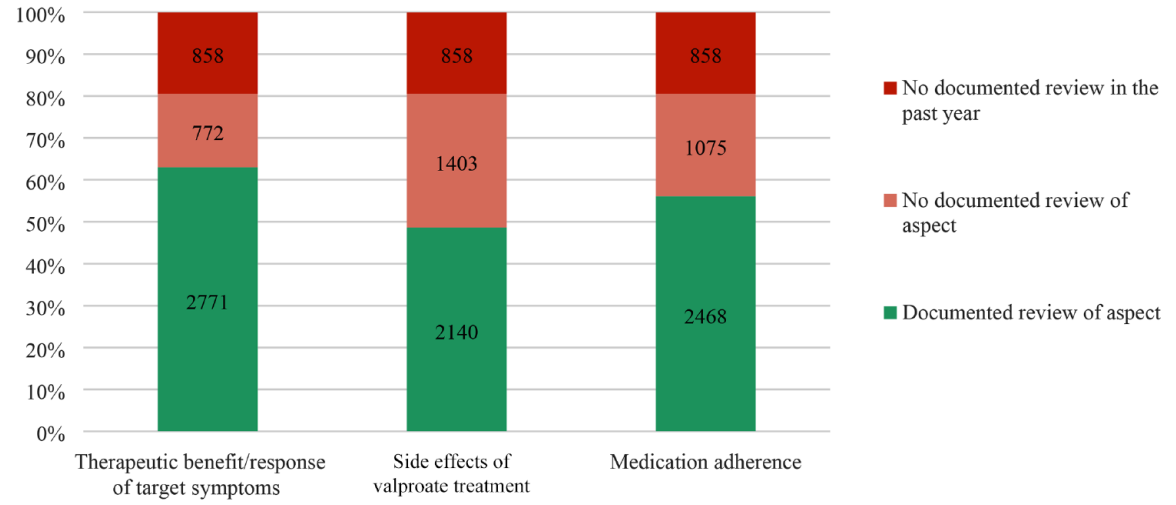

Figure 1. Documented review of therapeutic response, side effects and adherence in the past year: in a subsample of patients treated with valproate for more than a year ($n = 4401$).

(66%), body weight in 567 (62%), plasma glucose/HbA1c in 511 (56%) and plasma lipids in 510 (55%). With respect to meeting the clinical practice standard, an FBC, LFTs and a measure of body weight were all documented in 464 (50%) cases.

Early on-treatment review

Six hundred and thirty-one patients in the total national sample had been prescribed valproate for between 3 months and a year, allowing sufficient time for an early on-treatment review of the efficacy and tolerability of valproate to be conducted. Within this subsample, there was a documented early on-treatment review that addressed therapeutic benefit in 441 (70%), side effects in 332 (53%) and adherence in 372 (59%). A review of all three aspects was documented in 274 (43%) cases, thus meeting practice standard 4. There was no documented review of any of these aspects of valproate treatment in 147 (23%) cases.

Body weight had been measured in 244 (39%), LFTs in 245 (39%), an FBC in 244 (39%), plasma glucose/HbA1c in 193 (31%) and plasma lipids in 190 (30%); none of these physical health checks/measures were documented in 298 (47%) cases.

Review of continuing valproate treatment

Data relating to clinical review of continuing valproate treatment were collected for the subsample of 4401 patients who had been treated with valproate for more than a year. The proportions of patients for whom there had been reviews of efficacy, tolerability and adherence are shown in Figure 1. Review of all three aspects was documented in 1680 (38%) cases, meeting practice standard 5. There was no documented review in the last year of the efficacy or tolerability of this medication in 858 (19%) cases.

Details of the reviews of individual physical health checks/measures that were documented in the clinical records are provided in Figure 2.

Discussion

The information collected on the use of valproate in this large sample of patients under the care of adult mental health services revealed that the majority of such prescribing was long-term and off-label. The clinical rationale for prescribing valproate was not documented in the clinical records in more than a quarter of cases overall and the benefits and side effects had not been reviewed in the past year in two-fifths of cases receiving long-term valproate treatment.

Clinical reasons for prescribing valproate

In the United Kingdom, the licensed indications for valproate in the form of sodium valproate or valproic acid are restricted to the treatment of epilepsy while for the semi-sodium formulation the licence is limited to the treatment of manic

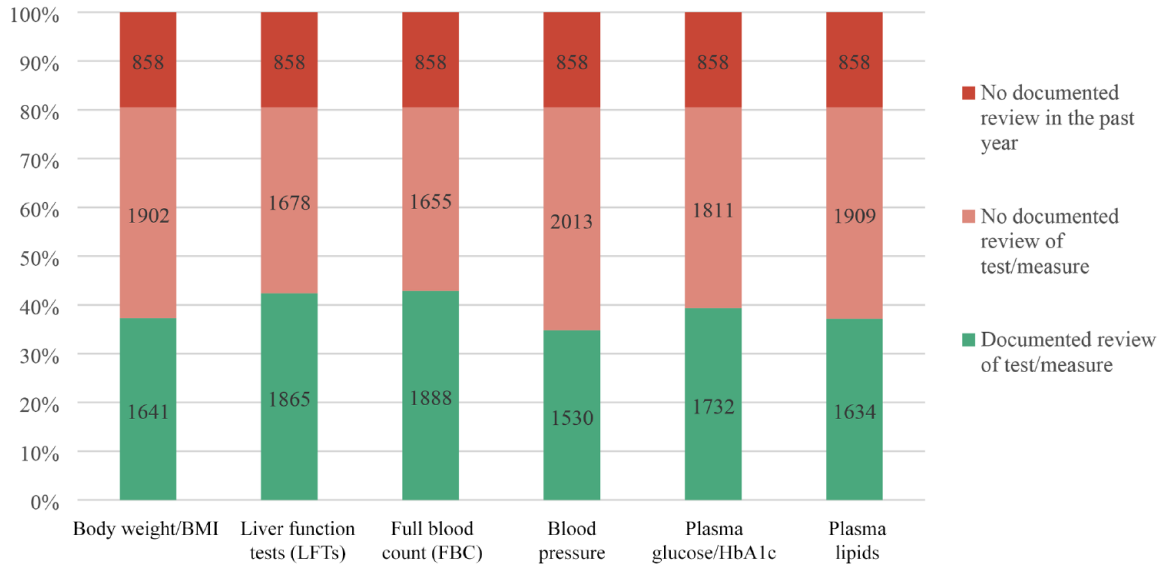

Figure 2. Documented physical health tests/measures conducted in the past year: in a subsample of patients treated with valproate for more than a year ($n = 4401$).

episodes in bipolar disorder when lithium is contraindicated or not tolerated and the continuation of treatment after a manic episode which has responded to this preparation. There are no double-blind, placebo-controlled trials investigating sodium valproate in bipolar disorder or semi-sodium valproate in epilepsy, so the efficacy and tolerability of these preparations for these indications have not been directly investigated, although differences would seem unlikely given that the active moiety of the sodium and semi-sodium preparations is the same. Taking the pragmatic view that any formulation of valproate could be assumed to have a supporting evidence base for the indications listed above, just over four patients out of every ten in our sample was prescribed valproate for one of these indications. A similar proportion was prescribed valproate for an indication that was clearly off-label, most commonly mood instability, problems of impulse control, aggression and refractory psychotic symptoms. This suggests that clinicians have extrapolated prescribing recommendations derived from the evidence base supporting the use of valproate in bipolar disorder and applied these to the management of other conditions in which mood symptoms are seen.

Four-fifths of our audit sample were older than 35 years of age, suggesting that relatively few were likely to have had a short duration of illness. Furthermore, other psychotropic medications were commonly prescribed in combination with valproate. Taken together, these findings suggest that valproate prescriptions tend to be targeted towards those with more established illness, where it is used as an adjunct to treat refractory symptoms. Such use increases the risk of drug–drug interactions and of prescribing cascades, where further medications are added to manage the side effects of existing medications.[16] For example, valproate-induced weight gain may contribute to the development of hypertension or dyslipidemia both of which are likely to require pharmacotherapy in their own right. Adverse effects may also be interpreted as new medical conditions prompting further investigations or tests. For example, valproate-induced alopecia or amenorrhea may result in onwards referral to dermatology or gynaecology, respectively. Also, valproate treatment can cause a false positive for ketones in urine,[3] potentially prompting a range of further medical investigations.

Schizophrenia

Almost half of the patients in our audit sample had a diagnosis of schizophrenia, which suggests that refractory symptoms in such patients are a common target for valproate treatment. This supports the findings from recent surveys and audits of prescribing practice where valproate was prescribed for between a tenth and a fifth of patients with schizophrenia, depending on the clinical setting.[4,5,17]

The rationale for prescribing valproate in the schizophrenia subgroup was to manage mood symptoms in three out of every five cases, while the management of refractory psychotic symptoms and persistent aggression were the reasons for one in ten and one in seventeen cases, respectively. More than a quarter of these patients had at least one other co-morbid psychiatric diagnosis. Where schizophrenia was the sole psychiatric diagnosis, almost a third were prescribed clozapine and more than half were prescribed two or more psychotropic medications in addition to valproate; furthermore, the median daily dose of valproate was higher in this subsample than in patients with a sole psychiatric diagnosis of bipolar disorder.

With respect to the recommendations in evidence-based clinical guidelines for the treatment of schizophrenia, NICE[18] did not review the evidence for adjunctive valproate and therefore do not make any recommendations regarding its use, while the BAP guideline[19] concludes that the evidence supporting valproate as an augmenting agent for refractory psychotic or mood symptoms or for the management of persistent aggression in schizophrenia is too limited to support a recommendation of routine use, but if valproate is used it should always be in the context of an individual therapeutic trial with careful monitoring of clinical response and side effects. This latter recommendation is compatible with the findings of a Cochrane review[20] that systematically examined the evidence for the use of valproate as an adjunct to antipsychotic treatment for refractory psychotic symptoms; based on data from open label and mostly short-term studies, a modest beneficial effect was found for valproate with respect to overall clinical response but this effect was not apparent in the only two studies of valproate augmentation (of non-clozapine antipsychotic medications) that used a double-blind design. The authors of this Cochrane review concluded that further 'large double-blind randomised trials should be undertaken to properly determine the clinical effects of adding valproate to antipsychotic treatment for people with schizophrenia'. One such study, testing the effectiveness of valproate as an adjunct to non-clozapine antipsychotic treatment for refractory psychotic symptoms, has just started recruiting in the United Kingdom.[21] With respect to the augmentation of clozapine with valproate, a systematic review and meta-analysis identified two relevant randomised controlled trials (RCTs), conducted in China with a total of 118 participants, suggested a large effect size (standardised mean difference (SMD) −2.36; −3.96, −0.75).[22] However, both trials were judged by the authors of the review to be of poor quality. Further adequately powered high-quality studies of valproate augmentation of clozapine are needed to determine the risk–benefit balance of such a strategy. Thus, the effectiveness of valproate augmentation of antipsychotic medication, whether non-clozapine or clozapine, remains uncertain.

There are no studies that specifically address the effect of valproate on mood symptoms in patients with schizophrenia although, in the Positive and Negative Syndrome Scale (PANSS),[23] which is commonly used in relevant studies, there are individual, mood-related items, such as 'grandiosity' and 'depression', that contribute to the overall rating scale score.

With respect to persistent aggression in patients with schizophrenia, there is most evidence supporting the use of clozapine[19] and this antipsychotic medication was prescribed for a third of the subsample with a sole diagnosis of schizophrenia. There are findings from some small open studies and small, very short-term, open randomised studies that suggest valproate augmentation of antipsychotic medication may reduce aggression in patients with schizophrenia, but so far there are no placebo-controlled RCTs.[20] Nevertheless, this limited evidence base has influenced practice; an international consensus survey of clinical experts in the Treatment Response and Resistance in Psychosis (TRRIP) working group found that almost nine out of every ten agreed or strongly agreed that mood stabilisers, albeit not specifically valproate, may be useful adjunctive treatments in patients with schizophrenia where persistent aggression had not responded to clozapine.[24]

The drivers for persistent aggression are of course wider than the content and intensity of hallucinations and delusions, with impulsivity, co-morbid personality disorder and substance misuse being relevant or perhaps wholly responsible in some cases.[25] But there are no studies that have explored the effect of valproate on persistent aggression associated with any of these specific drivers, if indeed such pure samples could be reliably identified and recruited to trials. Nevertheless, when the PANSS is used as a general outcome measure, any reduction in the 'hostility', 'tension', 'uncooperativeness' and 'poor impulse control' item scores would suggest an effect on aggression.

In our sub-sample where schizophrenia was the sole psychiatric diagnosis, the target behaviour for valproate treatment was persistent aggression for one in 17 patients. In such patients, the drivers for aggression are likely to be refractory psychotic symptoms, but the contribution of comorbid substance use and personality disorder that have not been formally diagnosed or that do not fulfil the diagnostic criteria cannot be excluded.

Bipolar disorder

Where the sole psychiatric diagnosis was bipolar disorder, the most common reasons for prescribing valproate were to treat an episode of mania or to protect against relapse into mania; both are licensed indications and both are supported by the current NICE[1] and BAP[2] guidelines for the treatment of bipolar disorder. Other reasons for prescribing valproate included the treatment of an acute episode of bipolar depression or the prevention of depressive relapse. While the evidence-based guidelines mentioned above do not support the off-label initiation of valproate specifically to treat an episode of bipolar depression, or to prevent relapse into depression, they do support increasing the dose or otherwise optimising the use of this medication if it is already prescribed. Our data therefore suggest that the use of valproate in patients with bipolar disorder is likely to be broadly consistent with the relevant recommendations in the NICE and BAP guidelines in the majority of cases.

That three-quarters of the patients with a sole psychiatric diagnosis of bipolar disorder were co-prescribed antipsychotic medication with valproate is consistent with the findings of a previous POMH QI audit that focused on the use of valproate for bipolar disorder; four-fifths of those prescribed valproate were also prescribed antipsychotic medication.[26] Furthermore, both the current and 2018 audits found a relatively low use of lithium in combination with valproate (14% and 11%, respectively) despite the stronger evidence base supporting the former, particularly for the prevention of relapse.[27] These findings suggest that prescribing for bipolar disorder in UK mental health services has been relatively consistent over the past few years.

Personality disorder

In the sub-sample of patients for whom personality disorder was the sole psychiatric diagnosis, the clinical reason for prescribing valproate in over half was to treat emotional instability, with impulsivity, persistent aggression and self-harm the treatment targets for between one patient in six and one patient in nine. While UK evidence-based clinical guidelines for the management of borderline personality disorder[28] and antisocial personality disorder,[29] and a Cochrane review of pharmacological interventions for antisocial personality disorder,[30] do not support the use of valproate for these indications, that this medication is relatively commonly prescribed for patients with personality disorder is consistent with the findings of a previous, large, POMH QI audit in the United Kingdom that examined prescribing practice for patients with emotionally unstable personality disorder.[6] The most likely explanation is that clinicians extrapolate from the evidence base supporting the use of valproate in the treatment of epilepsy and as a mood stabiliser in bipolar disorder to other indications that encompass mood instability, aggression or problems of impulse control. With respect to the latter, a Cochrane review addressing the use of antiepileptic medication for aggression and associated impulsivity[31] stated that although there is insufficient evidence to allow any firm conclusions to be drawn, there were limited data from a single RCT suggesting that valproate may be superior to placebo for persistent aggression in men with Cluster B (mostly antisocial and emotionally unstable) personality disorder.

Seven out of every ten patients with a sole psychiatric diagnosis of personality disorder in our audit sample were prescribed antipsychotic medication in addition to valproate and for one in six such cases the antipsychotic was clozapine. Furthermore, seven out of every ten such patients were prescribed two or more psychotropic medications in addition to valproate, suggesting that such patients are clinically complex and that the symptoms and behaviours that were being targeted by valproate treatment are likely to be treatment refractory, at least to some degree. However, the lack of evidence from well conducted, RCTs means that the effectiveness of the off-label use of valproate for symptoms and behaviours associated with personality disorder is uncertain. This places additional responsibilities on prescribers to ensure that any use of valproate for these indications should be an individual treatment trial that includes careful review of efficacy and tolerability.

Documentation that off-label use had been explained to the patient

Our audit data identified two QI issues. First, off-label use was not always recognised by prescribers, partly perhaps because the use of valproate to treat emotional dysregulation, persistent aggression and impulsivity is so established in clinical practice that prescribers are not aware that these are unlicensed indications. Second, where the prescription was recognised as being off-label, there was rarely any documentation in the clinical records to confirm that this had been explained to the patient.

This is in line with the findings of a survey of a small sample of psychiatric inpatients in a tertiary setting who were prescribed a mood stabiliser off-label.[32] While the psychiatrists who were providing care for these patients were generally aware that they were prescribing off-label, less than a third of the patients had had this explained to them and such an explanation was rarely documented in the clinical records. The most common reason given for not explaining off-label use was that the patient would have difficulty understanding the concept.

It is recommended that when using a medicine off-label, prescribers should satisfy themselves that there is sufficient evidence or experience of using the medicine for the intended purpose to demonstrate its efficacy and safety, and that the patient has been provided with sufficient information to enable informed consent to this treatment, including an explanation of off-label use as it relates to their care.[33,34] There are good clinical reasons for these recommendations. With respect to the first recommendation, the General Medical Council (GMC) is clear that prescribers are responsible for the prescriptions that they sign[33] and they must be satisfied that the medicines they prescribe serve the patient's needs. With respect to the second recommendation, patients may well become aware over time that their medication is being used outside its licensed indications. For example, the manufacturer's patient information leaflet that is packaged with the medication will refer only to the use of the medication for its licensed indications (the package insert for sodium valproate refers only to its use in the treatment of epilepsy). This realisation may be at best, confusing for patients and at worst, cause them to lose trust and confidence in their prescriber. Furthermore, it has long been known that those patients who feel that information about their medication has not been adequately shared with them may be less likely to adhere to their medication regimen.[35]

Physical health checks in the 3 months prior to starting valproate

Valproate is associated with a number of side effects including tremor, gastro-intestinal upset, dry mouth, transient hair loss and peripheral oedema.[3] However, two potential side effects, thrombocytopenia and hepatic damage, require blood tests to identify them and so a pre-treatment (baseline) FBC and LFTs are recommended by the manufacturers[3] and endorsed by NICE in its guideline for the management of bipolar disorder.[1] Given that valproate is commonly associated with weight gain, NICE[1] further recommends that body weight is measured prior to starting treatment. Each of these tests/measures was documented in around two-thirds of cases. In the remaining third, the clinical implications of missing baseline measures are that should any of the above clinical problems become apparent at a later date, it will not be possible to determine whether or not they are likely to be associated with valproate treatment.

Early on-treatment review

In the first 3 months of valproate treatment, there was no documented review of clinical response in almost a third of the relevant patient subsample and no review of treatment tolerability in almost half. Our data therefore suggest that the high prevalence of off-label use of valproate, where each prescription should be considered to be an individual treatment trial, does not seem to be associated with systematic review of efficacy and tolerability. Lack of such reviews makes it difficult to determine if there have been any benefits from valproate, and if so, whether these outweigh any side effects the patient has experienced. Medication that is not reviewed is likely to be continued by default, potentially exposing patients to a continuing side effect burden for uncertain therapeutic gain.

At least one of the relevant early on-treatment physical health checks had been documented in just over a half of cases. The extent to which these tests were conducted routinely or because a treatment-emergent problem was evident or suspected is unknown. But such targeted testing may not have been common as, for example, while weight

gain is a common and evident side effect of valproate treatment that can increase the risk of developing type-2 diabetes and cardiovascular disease, body weight was no more likely to be documented than any of the other physical health checks, such as LFTs. While it is recommended that LFTs are checked within the first 6 months of valproate treatment, it should be noted that severe valproate-induced liver injury is very rare and the established risk factors (receiving multiple anticonvulsant medications, young children, severe seizures and degenerative brain disease) are unlikely to be relevant in the vast majority of patients under the care of adult mental health services. These data suggest that, in current practice, tests/measures for side effects that could reasonably be expected to occur with valproate treatment are no more likely to be documented than tests/measures for side effects that occur far less frequently.

Review of continuing valproate treatment

For patients prescribed valproate for more than a year, there was a documented review of this treatment in the last year in four-fifths of cases but these reviews were often incomplete, with therapeutic response more likely to be documented than adherence or side effects. Given that for the majority of patients, the valproate prescriptions were for off-label or unclear indications and part of a complex medication regimen, incomplete and absent reviews could be seen as sub-optimal care.

The NICE guideline for the management of bipolar disorder[1] recommends that all patients who are prescribed valproate should have an annual check of body weight, LFTs and an FBC. Each of these tests/measures was documented for two patients out of every five. While LFTs and an FBC might reasonably be expected to identify side effects of valproate, albeit potentially serious ones, only rarely, tests/measures to detect increases in body weight and the consequences of this (hypertension, impaired glucose tolerance and dyslipidaemia) are much more likely to detect abnormalities that both contribute to increased cardiovascular risk and are potentially remediable. This suggests that the potential for valproate to cause metabolic side effects[36–38] may not be widely understood.

Conclusion

Valproate is commonly prescribed in mental health services for a variety of off-label indications, although there is a very limited evidence base for such treatment and the risk:benefit balance remains uncertain; essentially such prescribing has become ‘custom and practice’. Patients rarely receive an explanation that their valproate prescription is off-label, perhaps partly because the licensed indications are not widely understood by prescribers. Furthermore, valproate prescriptions are not routinely managed as individual treatment trials potentially exposing patients to ineffective and poorly tolerated treatment by default. Clinicians may like to consider systematically reviewing all patients under their care who are prescribed valproate and consider stopping such treatment where the clinical reasons for prescribing valproate or the benefits of continuing valproate treatment are unclear.

Strengths and limitations

- Given the large sample size and the submission of data by the vast majority of mental health Trusts, our findings are likely to be representative of prescribing practice in adult mental health services in the United Kingdom. However, they may not be generalisable to other clinical settings such as old age or learning disability services, or adult mental health services outside of the United Kingdom.
- We cannot confirm the methods used by Trusts to identify their audit samples. However, given the number of participating services, systematic bias would seem unlikely.
- All the audit data were systematically collected over the same time period, using a standard data collection tool.
- The sub-samples of patients with a single diagnosis of schizophrenia, bipolar disorder or personality disorder were large enough to allow analysis of the reasons for prescribing valproate by diagnosis.
- With respect to performance against the practice standards, the audit data were drawn primarily from documentation in the clinical records and some of the findings are therefore dependent on the quality of record keeping. For example, if the provision of an explanation to a patient about the off-label nature of their valproate prescription had not been documented, then it would not have been captured.
- The data collected pertained to why valproate was prescribed and how it was

monitored but did not allow for any judgement as to whether the use of valproate off-label was appropriate for any individual patient.

Ethics approval and consent to participate

Ethical approval and patient consent are not required for audit-based QI initiatives.

Consent for publication

Not applicable.

Author contributions

Carol Paton: Conceptualization; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Leslie Citrome: Conceptualization; Methodology; Validation; Writing – review & editing.

Emilio Fernandez-Egea: Conceptualization; Methodology; Validation; Writing – review & editing.

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Availability of data and materials

The aggregated dataset that supports these findings is not openly available. Membership agreements between POMH-UK and participating mental health services state that each mental health service owns its own dataset and that this will not be shared by POMH with any third party. POMH is restricted to reporting on analyses based on the aggregated national dataset.

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