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## Review

## Valproate, divalproex, valpromide: Are the differences in indications justified?

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## ABSTRACT

In many countries, valproate is indicated for epilepsy only, whereas its derivative divalproex (DVP) and valpromide (VPM) are indicated for bipolar disorders only. DVP is composed of sodium valproate and valproic acid (VA) in a 1:1 molar ratio and VPM is a prodrug completely hydrolyzed in the gastric tract to VA. Whatever the drug, the absorbed and active substance is the valproate ion. In this article, we reviewed the potential reasons that might justify these different indications. We performed a literature review of comparative studies of efficacy, pharmacokinetic parameters, side effects and costs for VPA, DVP, and VPM. We found only studies comparing VA with DVP. None of the eight efficacy studies found differences in epilepsy or mood disorders. The ten studies of side effects reported a difference in terms of gastrointestinal effects, but inconsistently. The United States (US) summary of product characteristics and kinetic comparison studies reported bioequivalence between DVP and VA, but a longer T<sub>max</sub> for DVP, likely due to its gastro-resistant galenic form. VPM summary of product characteristics and pharmacokinetic studies revealed a lower bioavailability (80% vs. 100% for VA) and a delayed T<sub>max</sub>. There is an additional cost for using DVP or VPM as compared to VA (respectively +177% and +77% in France). The differences in indications between valproate derivatives do not seem justified. Interchangeability between VA and DVP in bipolar disorders seems possible, at identical dosage. VPM would require a closer dosing schedule and a 20% reduction in dosage when switching to valproate.

## 1. Introduction

Valproic acid (VA), or 2-propylpentanoic acid (Fig. 1), is a compound first synthesized by Burton in 1882 [1]. Initially used as an organic solvent, its anti-epileptic effect was fortuitously discovered in 1962 [2]. In 1967, it was marketed in Europe for the treatment of epilepsy (under the name Dépakine®) and then in United States of America (USA) in 1978 [3,4] (under the name Depakene®). The anti-manic activity of valproate was discovered via valpromide (VPM), or 2-propylpentanamide, the primary amide and a prodrug of VA (Fig. 1). Initially developed as it showed a better efficacy in the treatment of epilepsy [5], VPM mood-stabilizing efficacy was discovered fortuitously in France at the end of the 60 s while it was being tested in individuals with bipolar disorders [6,7]. These observations led to its commercialization in

France in 1977. However, its use remained restricted in Europe to France and Italy. In early 80 s, based on the results observed with VPM, several research teams in the USA began to investigate the effect of valproate in the treatment of bipolar disorders [8,9]. As the patent on VA was due to expire in 1993, a new valproate derivative, the sodium divalproate (DVP), or divalproex sodium or valproate semisodium or sodium hydrogen bis(2-propylpentanoate) (Fig. 1) appeared in 1983. Initially developed to reduce the gastrointestinal side effects of VA used in epilepsy [10,11], DVP was commercialized for the treatment of manic episodes in patients with bipolar disorders [1].

DVP is composed of VA and its ionic form, sodium valproate, in a 1:1 molar ratio. In mice, VPM showed anticonvulsant properties 3–5 times superior to those of VA [15,16]. However, unlike in mice [17], VPM is completely hydrolyzed in the gastric tract to VA in humans. Only VA is

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absorbed, so that no traces of VPM are found in the blood or urine after oral administration [15,18,19]. Thus, whatever the valproate derivative orally administered in humans, the active circulating form is valproate ion [20]. VA, VPM and DVP therefore have identical pharmacodynamic characteristics. Yet, the different valproate derivatives do not bear the same indications. In USA and in France, VA is only indicated to treat epilepsy, unlike DVP and VPM which are only indicated in bipolar disorders (Table 1) [4,21–24]. Besides, despite the marketing of DVP and VA generics, DVP is still more expensive than VA. Moreover, given the numerous shortages of valproate derivatives, the question of their interchangeability is frequently addressed to which French Authorities reply that the difference in indications makes it impossible [25]. To understand these differences in indications and to investigate the possibility of interchangeability, we performed a literature review of comparative studies of efficacy, pharmacokinetic parameters, side effects and costs of VPA, DVP and VPM.

To date, valproate is used in nearly 150 countries to treat a broad spectrum of epilepsy. DVP is only commercialized in the EU in France (Dépakote®), Germany (Convulsofin®) and Portugal (Diplexil®) [27]. It is also commercialized in the UK and the USA (Depakote®). In EU, VPM is only commercialized in France and Italy (Dépamide®), and not in the UK or the USA.

## 2. Efficacy

Only 8 studies compared VA with DVP in terms of efficacy, and none with VPM. Three included individuals with epilepsy, the others involved the management of individuals with psychiatric disorders, mostly with bipolar disorders. Characteristics and outcomes of these studies are summarized in Table 2. In this review we only get interested in comparison in adults, but a few studies compared DVP with VA in children [47].

### 2.1. Epilepsy

Three studies compared the efficacy of VA with DVP in epilepsy [11, 42,43]. All evaluated the switch from DVP to VA in mg/mg equivalent. None found a difference between the average number of monthly

seizures before (under DVP) and after (under VA). However, these studies had a prep-post, retrospective and open-label design, had no control group and very small sample sizes (between 7 [42] and 46 [11] patients). They therefore had potential biases that precluded definitive conclusions.

### 2.2. Bipolar disorders and other psychiatric conditions

The other efficacy comparison studies included individuals with psychiatric disorders. Some included only individuals treated for bipolar or other mood disorders [38,42,45], while others also included individuals treated for behavioural disorders [41,45,46]. Studies comparing efficacy in these conditions had three different methodologies: before/after (prospective or retrospective) comparisons of switching individuals from DVP to VA [41,42,45], retrospective cohort analyses of individuals on either DVP or VA [35,46] and a single parallel prospective comparative study [38]. Criteria for determining efficacy were the Clinical Global Impression (CGI) or a derivative score [41,42, 46], the rate of switch or interruption of therapy specifically for lack of efficacy [45,46] or the length of hospitalization or the rate of rehospitalization [35,41,45]. Only one study used the Young Mania Rating Scale (YMRS) and the Hamilton Rating Scale for Depression (HRSD) score [38].

Of the three pre/post studies evaluating DVP to VA switch, two had a similar design [41,42]. They were performed retrospectively, with small samples ( $n = 28$  and  $47$ ) of individuals treated for several different indications (mood or behavioral disorders) and the efficacy was measured by the CGI score. None found a difference in clinical score, but the small sample sizes and the use of the CGI score in open-label studies represent potential limitations. The third study [45] included a much larger number of individuals ( $n = 9260$ ) in a prospective way over a 6-year period after monotherapy instauration ( $n = 2232$  on DVP and  $n = 7028$  on VA), regardless of the type of psychiatric disorders. It is the largest comparative study between DVP and VA but it still may be hampered by some methodological issues. There was no randomization at inclusion and the choice of the molecule to introduce was left to the physician and varied from one service to another. Populations of the two groups were therefore not comparable, which required the authors to

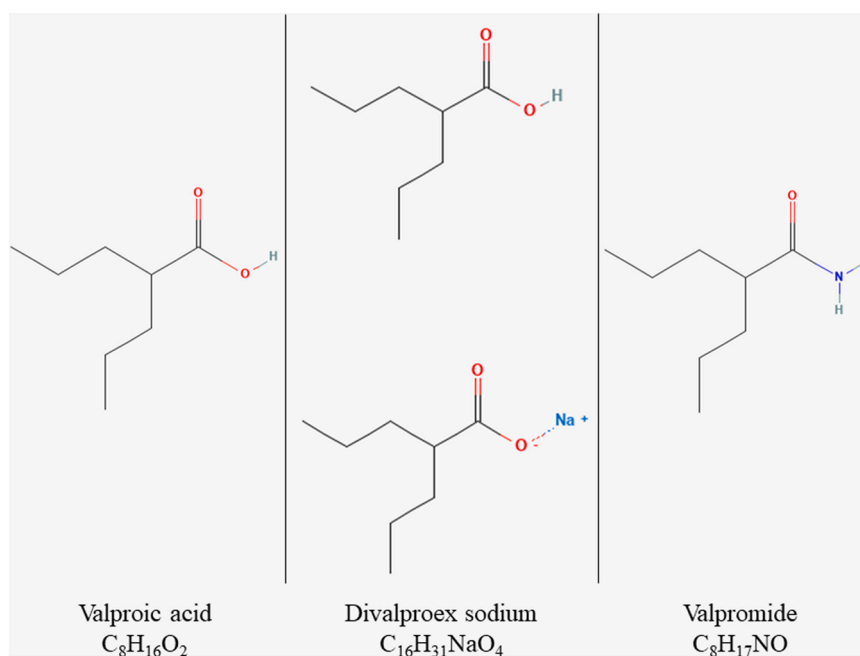


Fig. 1. Valproate derivatives. From PubChem [12–14].

**Table 1**

Approved indications for valproate derivatives in some countries (based on the summaries of product characteristics of each countries [26–33]).

	Valproic acid		Divalproex		Valpromide	
	Epilepsy	Bipolar disorders	Epilepsy	Bipolar disorders	Epilepsy	Bipolar disorders
<b>European Union</b>						
<b>France</b>	Yes	No	No	Yes	No	Yes
<b>Germany</b>	Yes	No	Yes	No	Not commercialized	
<b>Italy</b>	Yes	Yes	Not commercialized		Yes	Yes
<b>Portugal</b>	Yes	Yes	Yes	Yes	Not commercialized	
<b>USA</b>	Yes	No	Yes	Yes	Not commercialized	
<b>United Kingdom</b>	Yes	No	No	Yes	Not commercialized	
<b>Canada</b>	Yes	No	Yes	Yes	Not commercialized	
<b>Australia</b>	Yes	Yes	Not commercialized		Not commercialized	

control some variables. In addition, treatment indications were neither detailed or taken into account in the analysis. DVP patients had a 1.7 days longer initial hospital stay (14.9 vs 13.2 days), but rehospitalization rates and switching of therapy due to lack of efficacy were not significantly different between the two groups over the 6-year study period. Two studies retrospectively analysed medical records of individuals newly treated with either DVP or VA. No difference in efficacy was found after analysing the records of 300 individuals (n = 150 for VA and n = 150 for DVP), but several different psychiatric disorders were involved, not equally distributed between groups [46]. Another analysis of 18-month data of 4264 individuals treated as monotherapy (n = 588 with DVP and n = 4036 for VA) found no difference in terms of hospitalization risk for bipolar disorder, time to hospitalization and time to switch of therapy [35]. However, individuals were included following a period under treatment without symptoms or side effects. This “clean period” selected individuals on whom the treatment by a valproate derivative was already effective and well tolerated, facilitating the demonstration of the absence of difference. Finally, only one study had a sufficiently robust design to unequivocally demonstrate a potential difference in efficacy between the two drugs, by being prospective, parallel, randomized and blinded, with quantitative clinical criteria such as Young Mania Rating Scale (YMRS) and Hamilton Rating Scale for Depression (HRSD), less subjective than the CGI scale. Unfortunately, with only nine individuals included and two who completed the study, no conclusions can be drawn [38].

### 2.3. Conclusion

Few studies compared the efficacy of DVP versus VA, which all have several limitations. Pre/post and retrospective comparisons with individuals already stable, the use of CGI as efficacy criteria, and very small sample sizes weaken the conclusions of these studies. However, none of them found even a trend towards a difference in efficacy between DVP and VA, either in epilepsy or in psychiatric disorders.

### 3. Side effects

Ten studies compared side effects observed with DVP and with VA. Characteristics and outcomes of these studies are summarized in Table 2. As for efficacy, side effects comparisons were performed after switching from DVP to VA [11,41–43,45] or retrospectively on data from individuals treated by DVP or VA [35,44,46]. None compared VA or DVP to VPM. Almost all focused on gastrointestinal reactions, except

one that found only less lethargy in patients switched to VA [43], and another that found no difference in general tolerance (all reactions combined) [41,46]. One study found no difference in gastrointestinal side effects between DVP and VA [43]. Two studies found gastrointestinal side effects were more important in VA than in DVP, but in the first they did not lead to more interruption of treatment or prescription of drugs to manage them [41]. In the second study, only one individual that had side effects required a switch back to DVP [44]. On the other, several studies reported less gastrointestinal side effects and less prescription of drugs to manage them, but not at a significant level [11,35,38,42], after switching from DVP to VA. Noteworthy the most informative study showed prospectively more switch of drugs due to side effects from VA to DVP than from DVP to VA. The difference in the rate of intolerance was 5.5% in favour of DVP [45]. This is supported by another retrospective epidemiological study showing 2 times less gastrointestinal side effects (14.7 vs 28.7) and 3 times less interruption of treatment for gastrointestinal disorders (4 vs 12.7%) with DVP than VA in patients newly treated [46].

Initial safety data which motivated the commercialization of DVP concluded to a better tolerance for DVP than for VA [10]. However, this study did not directly compare DVP with VA but tested DVP in individuals who had experienced side effects with VA. It thus represents a selection bias and does not necessarily indicate that DVP has fewer side effects. Later studies did not systematically report better tolerance of DVP, on the contrary. Of the two most robust studies, DVP seemed to induce more gastrointestinal side effects than VA. However, two points must be considered. First, all comparisons used VA, never the valproate form. Deprived of its acid character, the valproate form might not show the same gastrointestinal side effects. Yet, the valproate form is commercialized in most countries, especially among the European Union. Secondly, the compared drugs had not the same galenic form. As of today, DVP was in an enteric-coated form while VA was in an immediate release form. Thus, side effects with VA might be due to the galenic form and the location of release of the molecule (further into the gastrointestinal tract with DVP), rather than to the chemical form. It should be noted that, except for one study, all focussed on gastrointestinal side effect, thus with no clear conclusion possible about non-gastro-intestinal side effects.

**Table 2**

Comparative studies of efficacy, side effects, pharmacokinetics and costs between divalproex (DVP), valproic acid (VA) and valpromide (VPM).

Authors, year and reference	Study Type	Population	Treatment comparison	Main outcomes				Limitation
				Efficacy	Side effects	Pharmacokinetics	Costs	
Bialer et al. [19,34]	Pharmacokinetic	N = 6 Healthy volunteers	VA vs VPM Single dose on the same patients			Tmax DVP (9 h) > VA (4.2 h) VPM bioavailability = 79% Same residual concentration No VPM detected in plasma		
Cranor et al. [11]	Retrospective Pre-post	N = 46 Epilepsy Adults mentally retarded Inpatients	DVP → VA (1 mg/1 mg) Patients stable for 3 months with DVP Follow-up during 18 months	Treatment continued in 89% (41/46) patients No difference in number of seizure (per month)	\ (not significant) in number of patients with GI SE and in prescription of drugs to manage GI SE		\ 56% (including drug cost, SE managing, global care)	Retrospective non-randomized non-parallel open-labelled Small samples Clinically stable patients
Iqbal et al. [35]	Retrospective Parallel	N = 4624 Bipolar disorders Outpatients	DVP (N = 588) vs VA (N = 4036) Min. 6 months of monotherapy Follow-up during 18 months	No difference in hospitalization rate No difference in time to interruption or switching of therapy (because inefficacy) No difference in time to hospitalization	No difference in time to interruption or switching of therapy (because SE)	No change in mean daily dose		Retrospective non-randomised open labelled Patients stable for 6 months
Dutta and Reed [36]	Comparison of pharmacokinetic studies	N = 9–15 Healthy volunteers	5 different formulations VA syrup VA capsule DVP sprinkle capsule DVP enteric-coated DR tablet DVP ER tablet			Tmax VA syrup (0.9 h) < VA capsule (2.2 h) < DVP capsule (5 h) < DVP DR (5.4 h) < DVP ER (19.7 h) Absolute bioavailability = 100% for all formulations except DVP ER (89%)		Comparison of isolated studies Different formulations between molecules
Garikipati et al. [37]	Pharmacokinetic	N = 36 Healthy volunteers	VA DR capsule vs DVP DR tablet			Tmax DVP (3.7 h) > VA (2.3 h) Bioequivalence of the 2 formulation (AUC <sub>0–t</sub> , AUC <sub>0–∞</sub> et Cmax)		Different formulations between molecules
Kablinger et al. [38]	Prospective Parallel Double blinded Randomized	N = 9 Bipolar type I Outpatients	DVP (N = 5) vs VA (N = 4) Newly diagnosed patients Follow-up during 6 months	DVP improves YMRS score (not significant) VA improves HRSD score (not significant)	No difference in SE number			Very small samples → impede statistical comparison
Loiseau et al., [54]	Pharmacokinetic	N = 102 Healthy subjects and epileptic patients Inpatients and outpatients	DVP or VA Single doses or chronic treatments			Tmax DVP (3–6 h) > VA (1–4 h) Same ratio dose/plasma residual concentration		
Pisani et al. [18]	Pharmacokinetic	N = 89 Epilepsy Inpatients	VA (N = 47) vs VPM (N = 42) Patients treated for at least 2 months			\ plasma concentration fluctuations for VPM Tmax VPA (2–4 h) < VPM (6–10 h) Only traces (<1 µg/mL) of VPM found in plasma Tmax VPA (1–2 h) < VPM (5–14 h) Identical half life Cmax VPA > VPM VPM bioavailability = 81.2% \ plasma concentration fluctuations for VPM Same residual concentration		
Pisani and Di Perr [39]	Pharmacokinetic	N = 8 Healthy volunteers	VA vs VPM single dose on the same patients (1 week interval)					

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Table 2 (continued)

Authors, year and reference	Study			Main outcomes				Limitation
	Type	Population	Treatment comparison	Efficacy	Side effects	Pharmacokinetics	Costs	
Schumock et al. [40]	Medico-economic Payer perspective	Bipolar disorders	Estimation of pharmaceutical and medical costs of DVP ER vs VPA prescriptions				Treatment cost: 646 \$/year for VA < 2416 \$/year for DVP (based on 1500 mg/d) Expected total cost: 34,209 \$/year for VA > 25,336 \$/year for DVP	Costs evaluated based on probability of success and SE occurrence estimated by a psychiatrist panel, not from measured data
Schwartz et al. [41]	Retrospective Pre-post	N = 28 21 behaviour disorders 7 mood disorders Inpatients	DVP → VA (1 mg/1 mg)	No difference in CGI score	More GI SE after switch No difference in interruption or switching of therapy (because SE) No difference in use of drugs to manage GI SE	↗ in daily dose (1205 mg/d → 1554 mg/d; +29%) No difference in serum concentration (after daily dose ↗)	DVP = 1163 \$/yr/pat VA = 133 \$/yr/pat	Retrospective study, non-randomized, non-parallel, open-labelled Several different pathologies Small samples Efficacy measured with CGI score (subjective)
Sherr and Kelly [42]	Prospective Pre-post	N = 47 25 mood disorders 20 behaviour disorders 7 epilepsy Inpatients	DVP → VA (1 mg/1 mg) 4 weeks DVP before switch 2 weeks and 6 months follow-up	No difference in CGI score No difference in seizure number	↘ (not significant) in number of patients with GI SE	No change in mean daily dose (≈1500 mg/day) Significant ↘ in serum concentration (69→59 µg/mL; -14%)	↘ 83% 905\$ saved/yr/patient	Non-randomized, non-parallel, open-labelled Several different pathologies Small samples Efficacy measured with CGI score (subjective)
Vadney et al. [43]	Prospective Pre-post	N = 77 Mental retardation and seizure disorders Inpatients	DVP → VA Follow-up during 8 weeks	No difference in seizure control Some change in psychiatric symptoms (but described as well tolerated)	No difference in GI SE, weight change, behaviour, appetite ↘ in lethargy ↗ in diarrhea			Non-randomized, non-parallel, open-labelled Several different pathologies No details in pathologies and psychiatric symptoms No details on methodological and data (letter to the editor)
Wagner et al. [44]	Retrospective Pre-post	N = 98	DVP → VA		4 patients with GI SE 1 switch back to DVP (due to SE)	No difference in serum concentration		No details on methodological and data (letter to the editor)
Wassef et al. [45]	Prospective Parallel	N = 9260 Psychiatry	DVP (N = 2232) vs VA (N = 7028) Newly treated patients Follow-up during 6 years	Length of stay DVP > VA (14.9d vs 13.2d; +1.7d; +15%) No difference in rehospitalisation rate No difference in the number switching of therapy (for efficacy reason)	Number of switching of therapy for SE VA > DVP (+5.5%)	No change in mean daily dose	Savings of one-third of inpatient costs and two thirds of a billion dollars yearly in medication costs	Non-randomized, open-labelled No details on diseases
Wilder et al. [10]	Prospective Pre-post	N = 27	VA → DVP Patients who could not tolerate VA (GI symptoms)		85% (23/27) tolerated DVP and continued therapy	Tmax DVP (3 h) > VA (1 h) Equivalent bioavailability		Non-randomized, non-parallel, open-labelled Inclusion of patients not tolerating VA only Small samples No details on diseases

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Table 2 (continued)

Authors, year and reference	Study Type	Population	Treatment comparison	Main outcomes				Limitation
				Efficacy	Side effects	Pharmacokinetics	Costs	
Zarate et al. [46]	Retrospective Analyst blinded	N = 300 Randomly selected from 3648 patients newly treated with DVP (3260) or VA (388)	DVP (N = 150) vs VA (N = 150)	No difference on a 4-point efficacy scale No difference on interruption of therapy for inefficacy	No difference on overall SE GI SE DVP < VA (14.7 vs 28.7%) but no difference in use of drugs to manage GI SE Interruption of therapy due to SE DVP < VA (4 vs 12.7%)	No difference in mean dosage (1185–1272 mg/d) No difference in serum concentration (61–64 µg/mL)		Several different diseases, not equally distributed between groups

CGI: clinical global impressions; DR: delayed release; ER: extended release; GI: gastrointestinal; HRSD: Hamilton Rating Scale for Depression SE: side effects; YMRS: Young mania rating scale.

## 4. Pharmacokinetics

### 4.1. Divalproex

#### 4.1.1. Comparison of summaries of product characteristics

Pharmacokinetic sections of Depakote® and Depakene® US prescribing information are strictly identical [4,24]. The prescribing information state that “equivalent oral doses of Depakote® (sodium divalproex) products and Depakene® (valproic acid) capsules deliver equivalent quantities of valproate ion systemically”. Surprisingly, each of them mentions a Tmax for both tablet and capsule forms, whereas a tablet form exists only for DVP (Depakote®) and a capsule form exists only for VA (Depakene®). Prescribing information note a difference in Tmax between the 2 drugs (4 h for tablet/Depakote® and 3.3 h for capsule/Depakene®), which therefore seems to be solely due to the galenic form. Moreover, we noted an incoherence in prescribing information, as the one for Stavzor® (a delayed release capsule form of valproic acid), indicates a Tmax of 2 h [48], shorter than Depakene® (an immediate release form). For the rest of pharmacokinetics, the three approvals report identical information concerning plasma clearance (0.56 L/h/1.73 m<sup>2</sup> for total valproate and 4.6 L/h/1.73 m<sup>2</sup> for free valproate), volume of distribution (11 L/1.73 m<sup>2</sup> for total valproate, 92 L/1.73 m<sup>2</sup> for free valproate) and mean half-life (from 9 to 16 h). In France, the pharmacokinetic parts of VA and DVP summaries of products characteristics are strictly identical but do not give any indication on Tmax [21,22].

#### 4.1.2. Comparative studies

Some studies comparing efficacy and side effects also focused on pharmacokinetic characteristics [10,35,41,42,44–46], however some compared the compounds specifically on pharmacokinetic characteristics [36,37]. Characteristics and outcomes of these studies are summarized in Table 2.

Regarding the effective dosages, results diverge. On study reported that patients switched from DVP to VA had a 14% decrease in residual valproate concentration (at 12 h after intake) after two weeks [42]. Consistently, another study reported the need to increase the dosage from 1205 mg/day to 1554 mg/day (29% increase) to maintain serum concentrations [41]. However, some studies found identical dosage (in mg/d) between VA and DVP to maintain clinical efficacy [35,44,45] and serum concentration [46].

DVP and VA were early demonstrated to be bioequivalent [10], with delayed absorption with DVP such that serum concentration peaked within 1–2.3 h with VA and 3–3.7 h with DVP [10,37]. The most interesting comparison of pharmacokinetics is that of Dutta and Reed (2007) [36], who compiled kinetic comparison studies of 5 different

formulations of valproate derivatives available on the US market in 2006: two VA immediate release forms and DVP immediate, extended and delayed release forms [49–51]. VA had a quicker absorption, even than immediate release DVP form. However, VA forms (syrup or liquid filled capsule) were faster-releasing than immediate release DVP form (capsule containing enteric-coated particles). The absolute bioavailability of all formulations is 100%, except for DVP extended release which is 89% [52].

### 4.2. Valpromide

As a prodrug of VA [15], VPM characteristics after absorption (plasma clearance, volume of distribution, plasma protein binding, half-life) are identical to other valproate derivatives and only characteristics related to absorption differ. The need for VPM to be hydrolyzed prior to its absorption affects its bioavailability, Cmax and Tmax and gives it absorption a high inter-individual variability [18,19], especially depending on the state of the digestive system. This variability is well illustrated by a case report of an individuals with resection of the small intestine with high dosages of VPM but low valproate serum concentrations due to the defect of hydrolysis enzymes. After a switch to VA, lower doses were necessary to get a higher plasma concentration [53]. Four studies compared VA and VPM on their pharmacokinetic properties [18,19,39,54]. They all found a delayed absorption for VPM with Cmax reached in 5–14 h compared to 1–4 h for VA. Cmax is also decreased of about 41% for VPM [18,19]. The residual plasma concentration was identical between VA et VPM [18,19,39,54], but VPM bioavailability was 77–81.2% depending on the galenic form, whereas VA bioavailability was near to 100% [19,39].

### 4.3. Conclusion

All three molecules are absorbed and found in the blood as valproate ion. Their pharmacokinetic characteristics differ only because of the difference in absorption. DVP and VA are therefore bioequivalent. The decrease in serum concentration reported in some studies when switching from DVP to VA at constant dosage did not systematically lead to a clinical difference. Pharmacokinetics comparison studies report a lengthening of Tmax and a decrease in Cmax with DVP. However, galenic forms of DVP and VA were different in all studies, as for today. Even in immediate release, DVP has an enteric-coated form, which will release the drug further into the digestive tract and delay its absorption. The difference in pharmacokinetics is therefore mostly due to the difference in galenic form than to the chemical form. VPM has a lower bioavailability, Cmax and Tmax than VA. Thus, as several authors already concluded it [19,53,55], VPM pharmacokinetics characteristics

are close to that of a delayed-release form of VA. As VA bioavailability is 100% and VPM is 80%, the switch from VPM to VA would require a 20% dosage increase.

## 5. Costs

### 5.1. Comparative studies

Few studies compared costs associated to individuals with bipolar disorders treated with VA or DVP. Characteristics and outcomes of these studies are summarized in Table 2. These studies performed more than 20 years ago were carried out in the USA, which makes it difficult to extrapolate to the present time and to all countries. However, they suggested saving costs when switching from DVP to VA, both in terms of drug cost (VA being less expensive than DVP) [11,42,44], but also by considering the management of gastrointestinal side effects [11]. In 2000 in the USA, DVP was 12 times more expensive than VA for an equivalent mg dosage [41]. Therefore, even taking into account a potential increase in costs related to treatments to reduce side effects, switching to VA resulted in 56% [11] to 83% [42] cost savings, i.e. about \$900 to \$1000 per patient per year [41,42]. Only one medical-economic study did not support this, estimating a total cost per patient of \$34,208.84 for VA and \$25,336.13 for DVP (including medical and pharmaceutical costs) [40]. However, probabilities of side effects occurrence and treatment success used to assess the costs were estimated by a psychiatrist panel, which leaved a great deal of subjectivity. They attributed to VA a treatment failure risk much higher than with DVP (55% vs 42%). Finally, Wassef et al. estimated that switching all individuals with psychiatric disorders from DVP to VA would save two thirds of a billion dollars annually [45].

### 5.2. Current costs comparison in France

Based on current French prices [21–23,56], we compared the difference in medication costs of individuals treated for bipolar disorders with DVP, VA or VPM. Based on equivalent dosages of 1,500 mg/d (corresponding to 25 mg/kg/d for an adult weighing 60 kg), Dépakine® (sodium valproate) costs between €142 and €161 per year, Dépakote® (sodium divalproate) costs between €394 and €402 per year, Divalcote® (a newly commercialized generic form of sodium divalproate) and Dépamide® (valpromide) costs €252 per year (we did not take into account the potential increase in dosage necessary to compensate the decrease in bioavailability) (Table 3).

Thus, a treatment with Dépakote® is 2–3 times more expensive than with Dépakine®, i.e. an increase in cost of approximately €250 per year per individual. In a report of the French General Inspectorate of Social Affairs (IGAS) [57], the French Medicine Agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé – ANSM) stated that in 2014, 262,455 individuals were treated in France with Dépakote® for bipolar disorders. If all these patients were treated with Dépakine® instead, this would represent an annual saving of 66 million of euros per year. However, this economic consideration must be individually balanced if the increased cost of DVP therapy results in fewer adverse effects or an improvement in patient compliance compared to VA therapy.

## 6. Conclusion

Whatever valproate derivative is administered (VA, DVP or VPM), all are absorbed as valproate ion. The three molecules therefore have the same mechanism of action and the same pharmacodynamic properties. Our review of the literature found only a few differences in tolerance and kinetics between DVP and VA. However, in each comparison, DVP and VA were in 2 different galenic forms. These differences in tolerance and kinetics are therefore potentially due to the galenic form rather than the chemical form. Thus, it does not seem to justify the difference in

**Table 3**

Comparison of daily and annual costs of Dépakine®, Dépakote® and Dépamide® treatments.

	Number of tablets per package	Price per package (€)	Price per mg (cents of €)	Price (for 1500 mg/d)	
				Daily (€)	Annually (€)
Dépakine® 200 mg	40	2.33	0.029	0.44	160.6
Dépakine® 500 mg	40	5.25	0.026	0.39	142.4
Dépakote® 250 mg	30	5.49	0.073	1.10	401.5
Dépakote® 500 mg	90	32.5	0.072	1.08	394.2
Divalcote® 250 mg	30	4.04	0.054	0.81	295.7
Divalcote® 500 mg	90	23.35	0.052	0.78	284.7
Dépamide® 300 mg	30	4.14	0.046	0.69	251.9

Price data are from French summary of product characteristics [21–23,56].

indications between the three molecules and even less the difference in indications between galenic forms: in the United States, DVP delayed and extended release forms are indicated to treat mania, migraine and epilepsy whereas VA and immediate release DVP form are only indicated to treat epilepsy. In France DVP and VPM are only indicated to treat mania and VA only to treat epilepsy. Thus, in bipolar disorders, it may be possible to switch from DVP to VA without dose adjustment, and from VPM to VA by decreasing the dosage by 20% to reach the same plasma valproate concentrations. However, some authors state that, unlike in epilepsy management, valproate dosing is less important and should be performed only in specific cases: physiological conditions, multiple therapy, ineffectiveness, suspected side effects, lack of compliance, etc [20].

In addition to solve problems of frequent shortage we had to face in France in recent years, the interchangeability of these molecules would mean significant savings as the switch from DVP to valproate of all individuals with bipolar disorders in France would represent an annual saving of 62.5 million euros.

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## CRedit authorship contribution statement

**Clément Delage:** Conceptualization, Supervision, Writing – original draft. **Maeva Palayer:** Investigation. **Bruno Etain:** Validation, Writing – review & editing. **Monique Hagenimana:** Investigation. **Nathan Blaise:** Investigation. **Julie Smati:** Investigation. **Margot Chouchana:** Investigation. **Vanessa Bloch:** Validation. **Valérie C. Besson:** Conceptualization, Supervision, Writing – review & editing.

## Conflict of Interest Statement

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