Review Article

Molecular and Therapeutic Potential and Toxicity of Valproic Acid

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Valproic acid (VPA), a branched short-chain fatty acid, is widely used as an antiepileptic drug and a mood stabilizer. Antiepileptic properties have been attributed to inhibition of Gamma Amino Butyrate (GABA) transaminobutyrate and of ion channels. VPA was recently classified among the Histone Deacetylase Inhibitors, acting directly at the level of gene transcription by inhibiting histone deacetylation and making transcription sites more accessible. VPA is a widely used drug, particularly for children suffering from epilepsy. Due to the increasing number of clinical trials involving VPA, and interesting results obtained, this molecule will be implicated in an increasing number of therapies. However side effects of VPA are substantially described in the literature whereas they are poorly discussed in articles focusing on its therapeutic use. This paper aims to give an overview of the different clinical-trials involving VPA and its side effects encountered during treatment as well as its molecular properties.

1. Introduction

Valproic acid (2-propylvaleric acid, 2-propylpentanoic acid or n-dipropylacetic acid) (see Figure 1(a)), derived from valeric acid (Figure 1(b)) (naturally produced by valerian, *Valeriana officinali*s) (see Figure 1(c)), was first synthesized in 1882 by Burton [1]. It is a branched short-chain fatty acid, forming a clear liquid at room temperature, and whose half-life is 9 to 16 hours. For nearly a century, this molecule was used as a "physiologically inert" solvent for organic compounds. It was in 1963, during a study focused on molecules with potential anti-convulsive activity, in which VPA was used as a molecular carrier, that the pharmacological activity of VPA was demonstrated: VPA prevented pentylenetetrazol-induced convulsions in rodents [2–4].

In the human brain, VPA alters the activity of the neurotransmitter Gamma Amino Butyrate (GABA) by potentialising the inhibitory activity of GABA through several mechanisms, including inhibition of GABA degradation, inhibition of GABA Transaminobutyratre (ABAT), increased GABA synthesis, and decreased turnover [5]. Moreover, VPA attenuates N-Methyl-D-Aspartate-mediated excitation [6, 7] and blocks Na^+ channels, Ca^{2+} channels (voltage-dependent L type CACNA1 type C, D, N, and F), and voltage-gated K^+ channels (SCN) [8].

Besides its clinical use as an anticonvulsant and mood-stabilizing drug [9], VPA presents beneficial effects in clinical depression [10], absence seizures [11, 12], tonic-clonic seizures, complex partial seizures [13], juvenile myoclonic epilepsy [14], seizures associated with Lennox-Gastaut syndrome [15], migraine headaches, and schizophrenia. VPA as a therapeutic agent is commercially available as Depakote, Depakote ER, Depakene, Depacon, Stavzor, Mylproin, Ergenyl, Dipropylacetic acid, Myproic Acid, Dipropylacetate, and Convulex.

More recently VPA has been described as an HDAC inhibitor, resulting in an increased interest for its use in cancer therapy. Chromatin is formed of DNA packaged in nucleosome structures, constituted by 146 base-pair DNA sequence winding around an octamere of histones (two copies of each histone: H2A, H2B, H3, and H4) held in place by histone H1. The condensed form of chromatin (heterochromatin) is inactive in terms of transcription whereas the decondensed form (euchromatin) corresponds to an active form. The transition between euchromatin and heterochromatin is dependent upon two families of proteins: histone acetyl transferases (HATs), and histone

deacetylases (HDACs). It has been established that histone acetylation leads to relaxation of the nucleosome structure, releasing the DNA and allowing transcription. Inhibition of HDAC promotes decondensed chromatin formation, thereby promoting the expression of genes.
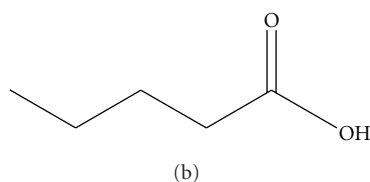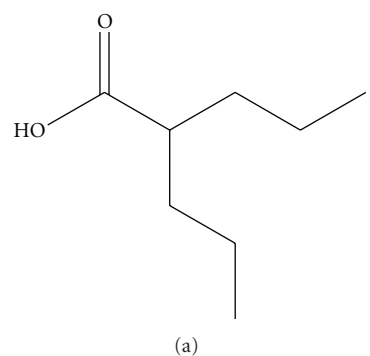
VPA, as well as other HDAC inhibitors (HDACi), is able to alter expression of many genes. Corresponding proteins were described to play important roles in cellular activity and could influence several important pathways such as cell cycle control, differentiation, DNA repair, and apoptosis [16–19].

VPA specifically targets 2 of the 4 classes of HDACs: class I, subclasses Ia and Ib, and class II, subclass IIa. Within subclass IIa, HDAC9 is an exception to this modulation, being activated by VPA, which is also true for HDAC11 [20]. HDAC 6, 8, and 10 are not modulated. It is interesting to mention that HDAC classes I and II have been reported to be strongly implicated in neuronal function, which could partially explain the action of VPA in neural pathologies.

DNA methylation also contributes to the regulation of gene expression. Hypermethylation of the promoter, usually corresponding to inhibition of gene expression, is controlled by DNA methytransferase (DNMT). Demethylation of nucleic acid has been commonly associated with passive processes corresponding to inhibition of maintenance methylation during S-Phase of the cell cycle. The existence of DNA demethylase was shown a decade ago, resulting in a demethylated active DNA form [21, 22]. HDACi have been associated with demethylation of DNA, and since 2001, were associated with the active demethylated form. The exact mechanism is not yet known, but it seems that VPA does not directly enhance the enzymatic activity of DNA demethylase. However, through HDACi activity, VPA enables methylated DNA to be more accessible, which is confirmed by the observation that inhibition of HAT diminishes the demethylation effect triggered by VPA [23, 24]. In addition, it has been shown that valproic acid downregulates expression of proteins essential for chromatin maintenance: SMCs 1-6 (Structural Maintenance of chromatin 1 to 6), DNMT1 (DNA methyl transferase-1), and HP1 (Heterochromatin Protein-1) [25]. The effects upon transcription are observed after less than 24 hours, while 48 hours are needed to see the effects upon protein levels, which correlates with DNA decondensation (shown in breast cancer cell lines).

Recently, it has been shown that VPA is also able to induce mono-, di-, or tri-methylation of histone 3, particularly at lysine 9 (H3K4) [20, 26–28]. Methylation of histones at this lysine is associated with increased transcriptional activity. However, this phenomenon and its purpose are not currently clear, considering the specific site of methylation, and the fact that it only occurs on already hyperacetylated histones, and near-demethylated genes. It is assumed that this modification could serve to stabilize the transiently released form of chromatin, mediated by histone acetylation [28].

Among many drugs named as "molecular therapies," epigenetic drugs are between the most encouraging, because in contrast to other drugs that target the expression of a molecule or a family of molecules, they target chromatin through associated proteins (HDAC, DNMT, HP1, and

(a)

(b)

Valeriana officinails flower
photo by Maarten.@2007 Erowid.org

(c)

Figure 1: (a) Structure of Valproic acid, (b) structure of valeric acid, (c) valeriana officinalis (valeriana officinalis in an early stage of flowering, [Belgium] Photo by Maarten. © 2007 Erowid.org: http://www.erowid.org/herbs/show_image.php?i= valerian/valeriana_officinalis_flower_.i2005e1334_disp.jpg).

SMCs). Thus, epigenetic drugs affect the expression of many proteins and therefore may be applicable to a wide range of pathologies, especially cancer, where multiple antioncogens are repressed during carcinogenesis. Epigenetic drugs could particularly target these repressed tumor suppressor genes.

Moreover, given that the balance of acetylation and deacetylation, under the control of HAT and HDAC, is not restricted to histones [29], it can be hypothesized that VPA, like other HDACi, could modulate molecular activity in addition to transcription. Targeted genes could be Ku (releasing BAX), STAT3, HSP90, p53, and various transcription factors. Candidates have already been mentioned in a preliminary study in 2005 [30].

For all the signaling pathways modulated, it has not been established if VPA acts through epigenetic regulation, inhibition of acetylation of molecules other than histones, or by other molecular mechanisms.

2. VPA Targets a Wide Range of Pathologies

Valproic acid used in therapy is available in many formulations: syrup, suppositories, tablets, or locale injection; the different formulations can affect the bioavailability and rate of absorption of the molecule. Classically age or weight has no influence in VPA serum concentration. There is no proportional relationship between the dose administered and the serum concentration [31]. Diet plays also a role in the rate of absorption as VPA is more rapidly bioavailable when ingested before feeding. Finally, the serum concentration can be strongly influenced by combination with phenytoin (49.5%), carbamazepine (66.2%), or phenobarbital (76.3%) than when given alone (100%). On average, 250 mg VPA ingested induce a serum concentration of 54.6 ug/mL (0.34 mM) [32]. Overdosage of VPA results in somnolence, heart block or deep coma.

2.1. Neurological Diseases. Many of the neurodegenerative diseases identified today have genetic causes. Spinal muscular atrophy (SMA) is caused by the homozygous loss of the SMN1 gene (survival motor neuron protein). The effects of the loss of this gene could be modulated by expression of the Fl-SMN2 protein (Full Length), which determines the severity of the disease [33]. VPA is a promising candidate for Fl-SMN2-overexpression therapies, because it has been shown that it is able to increase both SMN transcript and protein levels in SMA patients. However, the specificity of target of several HDACi members decreases their effectiveness and could lead to the choice of less specific molecules, such as SAHA [28].

Parkinson's disease (PD) is caused by the degeneration of nigrostriatal dopaminergic neurons. To date, several scientific papers have shown no effect of VPA on PD. However, recent *in vitro* studies have shown positive effects of VPA in models mimicking PD at different levels: VPA treatment prevents apoptosis induced by rotenone (inducing PD-like neurodegeneration); protects neurons from dopaminergic toxin 1-methyl-phenylpyridinium (MPP$^+$) by stimulating the release of trophic substances from glia; protects cultured dopaminergic neurons from over-activated microglia-induced degeneration by promoting microglia apoptosis and protects neurons by increasing α-synuclein expression and preventing its monoubiquitination and nuclear translocation [34–37]. In rodents, experiments show that selective alterations of α-synuclein caused by rotenone (decrease of the native protein and an increase in monoubiquitination in substantia nigra and striatum) are counteracted by long-term administration of VPA [38].

Past clinical trials had showed a lack of VPA activity in patients with Huntington's disease (HD) [39], which is surprising given that the molecular explanation for this disease involves excitotoxicity and reduced gene transcription due to decreased levels of histone acetylation. However, a recent study showed that using high doses of VPA (100 mg/kg/days) is capable of prolonging life expectancy and improving traction [40]. This study, based on tests conducted on the N171-82Q transgenic mouse model of HD, showed that following chronic intraperitoneal daily administration, VPA significantly improved the condition of mice, increasing the number of the surviving mice and reducing the decrease in motor activity, and this without exerting any noteworthy side effects upon behavior or striatal dopamine content at the dose administered. This study therefore recommends further clinical trials, based on increasing doses of VPA administered in mono- or polytherapy.

2.2. Addiction. The GABAergic system is involved in psychostimulant sensitization, and VPA can modulate central GABAergic neurotransmission. An initial study, conducted on mice, showed that multiple injections of VPA, administered consecutively after methamphetamine, could reduce the addictive behavior induced by this drug. However, this effect is not reproducible for cocaine-induced behavior [41]. These initial results indicated that these forms of addiction should not involve the same neural mechanisms. A clinical study of VPA use in treating addiction to various substances particularly targeted the stage of detoxification prior to treatment and rehabilitation. It was shown that a combination of Buprenorphine and VPA seems to be the most appropriate for detoxification, compared to the traditional combination Clonidine and Carbamazepine [42].

Several addictions, obsessive-compulsive disorders, and compulsive sexual behaviors have similarities in their processes, and, in the use of VPA, may find a possible therapeutic treatment.

2.3. HIV Infection. Histone deacetylase 1 (HDAC1) has been implicated in maintaining HIV in infected cells. The inhibitory action of VPA upon this protein makes it a good candidate for AIDS therapy. A study published in 2005 undertaken with four patients, showed that three of them treated with valproic acid in addition to highly active antiretroviral therapy (HAART), showed a reduction in latent HIV infection [43]. However, a subsequent study showed that VPA, alone and in a long-term treatment, is not sufficient to reduce the size of the HIV-1 reserve [44].

2.4. Other Pathologies. The possibility of using VPA in treatment of Duchenne Muscular Dystrophy, a skeletal muscle degeneration disease, was recently demonstrated *in vitro* and *in vivo* on mice mdx/utrn$^{-/-}$ [45]. This study showed that VPA is able to induce the Akt/mTOR/p70S6K pathway, through the induction of phosphatidylinositol 3-OH kinase (PI3K), resulting in lower collagen content and fibrosis, a decrease of hind limb contractures, an increase of sarcolemmal integrity, a decrease of CD8-positive inflammatory cells and higher levels of activated Akt in muscles.

3. VPA Targets Signaling Pathways in Cancer Cells

Epigenetic processes, such as histone deacetylation and DNA methylation, are known to contribute to the cancerous transformation of cells by silencing critical genes, leading to chemotherapy resistance. It has been hypothesized that HDACi act through a derepression or a stimulation of

silenced tumor suppressor genes [46–48]. Several data demonstrate the ability of these epigenetic drugs to modulate global gene expression in tumors (Figure 2).

VPA modulates expression of p21WAF1/CDKN1A [49], a CDK (cyclin dependent kinase) generally associated with cell cycle arrest in G1/S phase. VPA appears to induce an increase in the amount of p21WAF1 protein over 48 hours in AML cells, which is independent of p53 levels (whose expression is not modulated by VPA), but appears to be dependent on c-myc, whose mRNA and protein levels decrease in a dose-dependent manner during VPA treatment. Under VPA treatment, transcription of c-myc is dependent upon JNK/SAPK, and ectopic expression of c-myc, leading to more resistant cells in cell cycle arrest, shows the importance of this protein in VPA-mediated activity. In addition to this, while VPA treatment in the cell lines is followed by a decrease of c-myc and an induction of p21, it has been observed that in primary AML cells, only the systematic decrease of c-myc is maintained, without upregulation of p21 expression.

VPA-induced apoptosis, via the extrinsic pathway involving engagement of the caspase-8-dependent cascade, sensitizes cells to TRAIL/Apo2L-mediated apoptosis by increasing expression of DR4 and DR5 by 3- and 14-fold, respectively. In the absence of TRAIL/Apo2L, VPA is able to reduce the expression of antiapoptotic factors acting on both extrinsic and intrinsic apoptotic pathways, including c-FLIPs, proteins associated with DISC and Bcl-2/Bcl-X(L). When applied with TRAIL/Apo2L, VPA increased cell death and caspase-3 activity. These results were reproduced in AML, CLL, thoracic cancers, and hepatocellular carcinoma [50–53].

VPA induces Caspase-11 and FAS-L at the transcriptomic level, and Caspase-3 at the proteomic level during exposition [54]. Long treatment periods result in enhancement of Fas-dependent apoptosis associated with an overexpression of Fas and Fas ligand, and a central role in Bcl-2 inhibition [55].

It has been reported that VPA increased β-catenin levels through concentration-dependent inhibition of glycogen synthase kinase 3-β (and 3α) activity, and tau phosphorylation [56]. On one hand, this resulted in the inhibition of ubiquitination of β-catenin and on the other hand, in the inhibition of c-jun phosphorylation leading to an increase in the DNA binding activity of AP-1. Inhibition of β-catenin ubiquitination led to its translocation into the nucleus, and resultant upregulation of c-myc transcription.

The PI3-kinase/Akt pathway and Sp1 are involved in HSP70 induction by HDAC inhibitors, and induction of HSP70 by VPA in cortical neurons may contribute to its neuroprotective and therapeutic effects [57].

In medullary thyroid cancer (MTC) cells, VPA is able to modify the expression of Notch1, by increasing its expression, resulting in inhibition of the growth of these cells and the induction of apoptosis. These results along with the apparent tolerance of patients to VPA treatment have led to the suggestion to involve VPA being in future clinical trials on advanced medullary thyroid cancer [58].

PPAR signaling is involved in several biochemical regulation processes, including lipidic metabolism, differentiation, insulin sensitivity, and cell survival. VPA appeared to be a pan-activator of PPAR (both PPARα, also PPARδ and PPARγ) [59, 60]. This mechanism could be one factor favoring the teratogenic effect of VPA [60]. In contrast, it was reported that in neuronal cells VPA induced a significant decrease in PPARγ signaling [61]. These results highlight potential tissue-specific effects of VPA, as observed in several publications, and the difficulties in predicting its effects prior to clinical trials.

In similar fashion, HDAC3 is involved in inhibition of STAT3 phosphorylation [62]. This inhibition led to a decrease in the dimerisation of STAT3 and its translocation into the nucleus for transcriptional activation of many genes in a wide range of biological processes, including induction of immune response, oncogenesis, cell cycle control, development, cell adhesion, and differentiation [63]. HDAC3 is one of the direct targets of VPA, but until now no papers present data concerning the effect of VPA on the STAT3 pathway.

4. Clinical Trials with VPA

As previously mentioned, several reports have demonstrated the ability of epigenetic drugs to modulate global gene expression in tumors. In many cases, such drugs have moved into the first or second phase of clinical trials for treatment of various solid cancers or leukemia, and in cotreatment with several chemotherapeutic agents (Table 1).

VPA is used for many years in the treatment of convulsive seizures and in chronic treatment of epilepsy. Highlighting its HDAC inhibitory property and therefore its potential action on some cancers has made this molecule, already well known, a top candidate in new clinical trials.

Valproic acid has been implicated in more than two hundred clinical trials, sometimes in association with other drugs and involving various pathologies, ranging from mood disorders to cancers, through treatment of narcotic addictions, muscle disorders, and the ability to reduce viral load in AIDS patients (http://clinicaltrials.gov/).

However, concerning cancer prevention and therapy, a recent study on a population taking VPA over a long period (minimum 1500 g in the last 5 years) demonstrated that it had no significant effect upon prevention of cancer development [64] and thus is not eligible for chemoprevention.

4.1. Clinical Trial in Noncancerous Disorders. VPA has been used for many years as a treatment against epilepsy and convulsive disorders. Today, the majority of clinical trials involving VPA relate to neural pathology, applying to more than thirty different pathologies.

One clinical study aims to compare the antiaggressive efficacy of risperidone monotherapy versus risperidone in combination with valproate in patients suffering from schizophrenia. The random blind test, including 33 patients (16 with risperidone and 17 with polytreatment), was unable to show any significant difference between the treatments, except a higher capacity of patients under combination therapy to complete the study [65]. The use of valproic acid was investigated for its ability to improve mood stabilization. The blind clinical trial aimed to assess the capacity of lamotrigine or VPA to increase mood stabilization for patients with
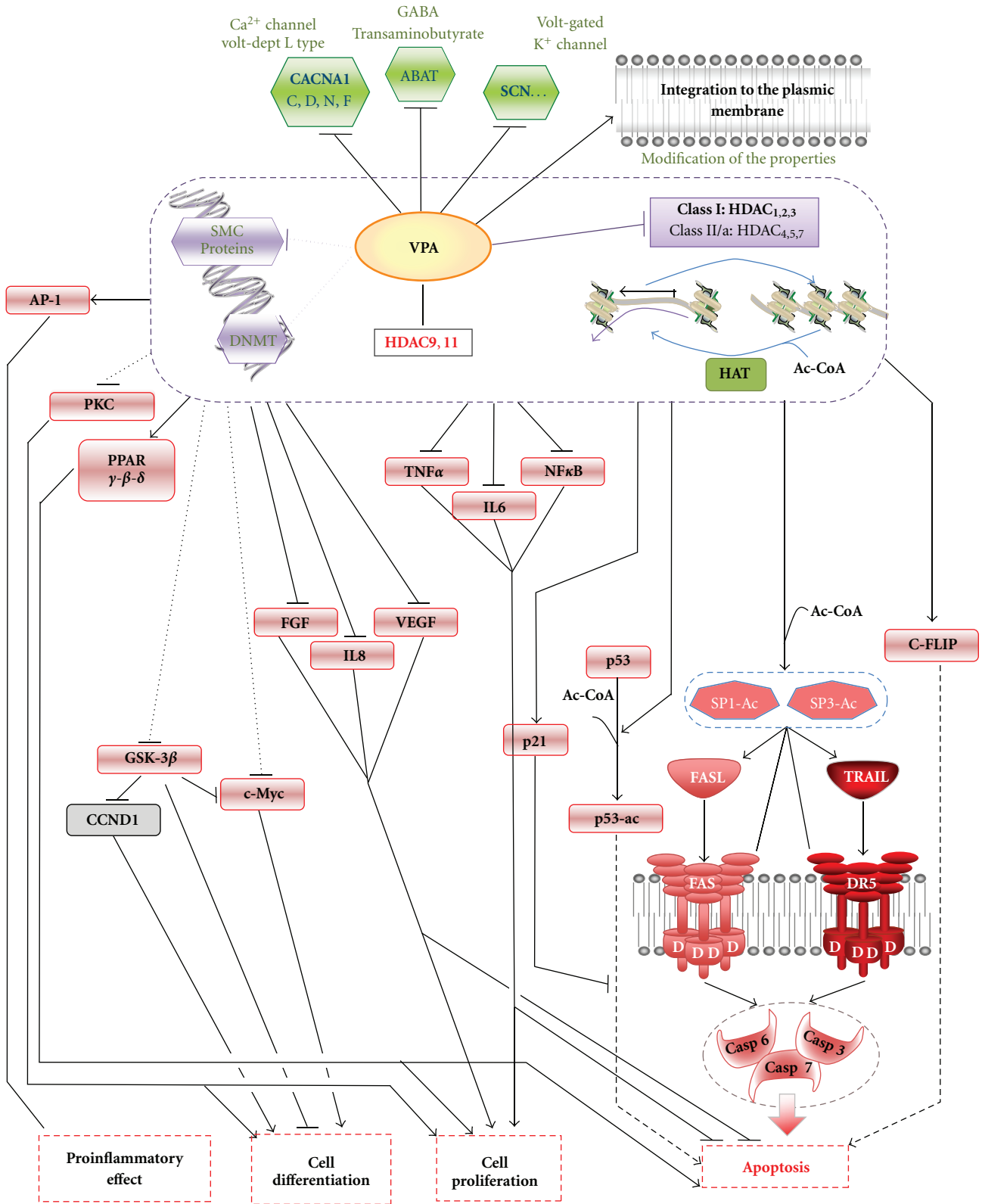
FIGURE 2: Pharmacological activity of VPA described in the literature. Schematic representation of direct and indirect targets of VPA. Principal direct targets known for VPA are ionic channels and ABAT (in green). Epigenetic action of VPA (in violet) as HDACi activity: VPA targets the transcriptomic system and principally directly inhibits HDAC class I (subcategories 1, 2, and 3), and less strongly class II/a (subcategories 4, 5, and 7), but induces HDAC 9 and 11, and indirectly inhibits the function of SMC and DNMT. Probably due to its epigenetic properties, or interactions not yet established, VPA alters, directly or indirectly, expression of many molecules involved in molecular pathways such as apoptosis, inflammation, differentiation, and proliferation (in red).

schizophrenia who are both stabilized and partially responsive [66]. Efficiency assessment was evaluated using the Positive and Negative Syndrome Scale, Calgary Depression Scale for Schizophrenia, Demoralization Scale, Clinical Global Impression severity and improvement scores and Lehman quality of life improvement scale to assess quality of life and social functioning. The increase of antipsychotics usage with mood stabilizers like lamotrigine or VPA for partially responsive patients with chronic schizophrenia seems to be an inefficient treatment strategy for improving the residual symptoms.

A clinical trial to establish the difference between VPA and Propranolol in the treatment of pediatric migraine prophylaxis was undertaken on a population of 120 patients aged from 3 to 15 years. The results showed no significant difference in all therapeutic effects between the two molecules, with a mean of 70% response and a reduction of >50% in headache frequency [67].

A clinical trial concerning agitation of older people with dementia was based upon the use of VPA as a treatment over several years, without any conclusive clinical trials able to show the effects. The results presented were based on the compilation of three incomplete clinical studies and show that VPA does not induce any improvement in pathology but does present an unacceptable rate of side effects [68].

Acute mania is a behavioral disorder outcome of bipolar disorder, also known as manic-depressive disorder, manic depression, or bipolar affective disorder. Compilation of data provided by European Mania in Bipolar Evaluation of Medication (EMBLEM) concerning the comparison of olanzapine and valproic acid treatments on a panel of over 600 patients ($n = 107$ valproate, $n = 514$ olanzapine), demonstrated that olanzapine monotherapy seems to be more effective than valproate monotherapy in the treatment of acute mania [69].

In contrast, a recent systematic review about the effect of VPA upon 142 patients with acute bipolar depression shows a significant effect of this molecule for the reduction of depressive symptoms of acute bipolar depression, as well as high patient tolerance [70]. The outcomes investigated were depression, anxiety, hypomania, attrition, and adverse events, and the study analyzed existing randomized control trial data for the efficacy and tolerability of valproate. Results are particularly conclusive for depression (50% improvement, for 22% of patients), but inconclusive for anxiety, and there was no evidence for an increased risk of mania, as it also induces long-term antidepressant effects.

VPA was investigated for clinical therapy of amyotrophic lateral sclerosis (ALS). This prognostic neuropathy was studied in 163 patients who received either VPA (1500 mg) or placebo, daily. The end points targeted were survival and progression of the disease. This study concluded that VPA had no beneficial effect upon survival or disease progression in patients with ALS [71].

A phase II study of the effect of VPA upon spinal muscular atrophy (SMA), with a panel of 2 SMA type I (ages 2-3 years), 29 SMA type II (ages 2–14 years), and 11 type III (ages 2–31 years) was recently published. The investigation focused upon several factors, such as assessment of gross motor function (via the modified Hammersmith Functional Motor Scale: MHFMS), electrophysiologic measures of innervations (with maximum ulnar compound muscle action potential amplitudes: CMAP) and motor unit number estimation (MUNE), body composition, and bone density via dual-energy X-ray absorptiometry (DEXA), and quantitative blood SMN mRNA levels, as well as carnitine depletion, hepatotoxicity, and increased weakness (for the side effects). Results revealed a trend of weight gain but also an increase of gross motor function in 27 patients, all of them with SMA type II and younger than five years old. There was no variation in expression of SMN protein (survival motor neuron protein), but bone mineral density and innervations increased significantly ($P \leq .0001$). In conclusion, the results presented by this preliminary study highlight the strengths and limitations of using a large cohort of patients for such a trial, as opposite results were obtained as functions of age and type of SMA. As such, no final conclusion was made concerning VPA, but it was suggested that additional controlled clinical trials with VPA targeting more restricted cohorts of subjects were needed [72].

A phase II clinical trial, principally investigating the effect of glyceryl trinitrate, and incidentally that of VPA, on pain caused by diabetic peripheral neuropathy, showed that these two molecules induce significant improvement, whether used alone or in combination [73]. This study, undertaken upon 83 patients divided into four groups, compared visual analogue score (VAS) and present pain intensity (PPI) at the beginning of the study and after three months, with motor and sensory nerve conduction velocities measured using electrophysiological tests. These results show significant improvements with both drugs individually and in combination, except for electrophysiological test results with VPA treatment, which show no significant modification.

Kaposi sarcoma (KS) is a cutaneous tumor caused by Human herpesvirus 8 (HHV8) and is often associated with coinfection by HIV (AIDS-associated Kaposi sarcoma), especially in African populations. Valproate stimulates HIV replication in some HIV-infected cell lines in culture [74, 75], and in the case of HHV8-infected cells, valproate induces expression of multiple HHV8-encoded transcripts that are associated with entry into the lytic phase of replication [76]. Because valproate is sometimes used in individuals who might be infected with HHV8 and HIV, a recent study aimed to identify the effect of VPA in cases of AIDS-associated Kaposi sarcoma [77]. Their results show that treatment with VPA was associated with low toxicity, and that KS clinical response and herpesvirus lytic induction were not high enough to be associated with significant induction of virus replication.

The clinical trials mentioned to date concerning treatment of nonmalignant diseases show few real benefits associated with use of VPA in mono- or polytreatment, and this despite the very encouraging preclinical data obtained so far.

Table 1: Ongoing clinical studies implicating valproic acid in monotherapies.

Dependences

    Alcohol abuse or dependence
    Alcoholism
    Cocaine dependence
    Marijuana abuse
    Substance abuse or dependence
    Substance withdrawal syndrome

Cancer

    Autoimmune lymphoproliferative syndrome
    Brain and central nervous system tumor
    Breast cancer
    CLL
    HTLV-I associated myelopathy
    MDS risk; AML
    Nasopharyngeal carcinoma
    Prostate cancer
    Sarcoma

Neurological disorders

    Alzheimer disease
    Amyotrophic lateral sclerosis
    Attention deficit hyperactivity disorder
    Autism
    Bipolar disorder
    Borderline personality disorder
    Cluster headache
    Dementia
    Depression
    Disruptive behavior
    Epilepsy
    Mania
    Migraine
    Mood disorder
    Neuralgia
    Phosphosensitive epilepsy
    Post traumatic stress disorder
    Progessive supranuclear palsy
    Resistant bipolar depression
    Schizophrenia
    Spinal muscular atrophy type 1

Others

    Asthma
    Hypersplenism; lymphadenopathy
    Hypoalbunemia
    Insulin resistance

4.2. Clinical Trial in Solid Tumors and Leukemia

4.2.1. VPA in Myeloid and Lymphoid Malignancies. The use of VPA in monotherapy or polytherapy seems promising for leukemia diseases. It has already been established that VPA exerts different effects in different cell types, and probably in the function of these cell types. It can induce proliferation in early stem cells and can inhibit angiogenesis, production of TNF-α and IL-6, and activation of NF-κB. Taken together these properties could be beneficial in the treatment of MDS or leukemic pathologies.

While HDACi are emerging as valuable new agents in the treatment of acute myeloid leukaemia (AML), the efficiency rates of these compounds in isolation are low, which requires them to be used in cotreatment with other anticancer drugs. Research into predictive markers of the efficiency of cotreatment with VPA gave rise to a study published in 2009, comparing results obtained by coprocessing using all trans retinoic acid (ATRA) and theophylline on 20 patients and several cell lines, and a microarray study on primary AML cells and cell lines. Comparison between results obtained with cotreatment (one Complete Remission (CR), two Partial Remission (PR)) and those obtained in treatment of primary cells and cell lines allowed the authors to conclude that similar factors determine both *in vivo* and *in vitro* sensitivity and identified elevated FOSB-expression as a potential marker of VPA sensitivity [78].

Hematological improvement was reported in many patients with different types of cancer following VPA treatment, with favorable responses; in patients with MDS (myelodystrophy syndromes) and MPS (myeloproliferative syndromes) [79]; in patients with AML developed from MPD (myeloproliferative disorders) [80]; in patients with myelofibrosis in myeloid metaplasia [81]. Clinical studies on the use of VPA have shown the beneficial effect of this drug especially on MDS [82, 83].

In 2007, a phase I/II study investigated the use of a tritherapy combination of 5-azacitidine (5-AZA), VPA, and ATRA in patients with acute myeloid leukemia or high-risk MDS. A total of 53 patients were treated with an age range of 5–84 years, and median age of 69 years. Maximum tolerated dose (MTD) for VPA was 50 mg/kg daily for 7 days, and toxicity consisted of reversible neurotoxicity. The overall response rate was 42% and was 52% for previously untreated older patients. This tritherapy combination is safe and presents significant clinical activity [84].

Another group studied whether VPA is active against myeloid leukemia in a polytherapy treatment associating VPA and ATRA, on 26 patients with low risk AML. The results showed that for the 19 patients with AML arising from MPD who completed four weeks of treatment, no CR was observed, one minor HI, and two PR in patients.

A recent phase II clinical study targeted 62 patients with high risk MDS, treated with a combination of 5-AZA and VPA. It showed that for the 26 patients who completed the eight cycles, 30.7% obtained complete or partial remission (CR or PR), 15.4% had major hematologic improvement (HI), whereas 38.5% showed stable disease (SD) [85]. VPA increased 5-azacytidine efficiency, and the study concluded that 5-AZA/VPA combined treatment is effective for patients with MDS with a poor prognosis.

The first results on the use of VPA in lymphoid diseases, made through a study of microarrays, are very encouraging, showing that this molecule is capable of

inducing apoptosis through repression of several antiapoptotic genes and induction of proapoptotic genes. Moreover, VPA significantly increased sensitivity to fludarabine, flavopiridol, bortezomib, thalidomide, and lenalidomide [86].

4.2.2. VPA in Solid Tumors.

VPA shows potent antitumor effect in a wide variety of cancers in preclinical studies, *in vitro* and *in vivo*, by modulating multiple pathways including cell cycle arrest, angiogenesis, apoptosis, differentiation, and senescence. These effects appear to be cell type-specific and could be dependent upon the degree of differentiation and, in the case of cancer, dependent upon the degree of alteration [87]. The majority of preclinical studies concerning the antitumoral effects of VPA were performed on myeloid or lymphoid leukemia. However, for solid tumors, some preclinical studies have provided interesting results. In 2008, Duenas-Gonzalez et al. [87] summarized the state of preclinical data and positive effects of VPA on 19 different types of solid cancer. In fibrosarcoma, cotreatment with VPA strongly increased the efficiency of hydralazin, and was able to eliminate residual disease tissue after surgery or treatment in xenograft models [88]. In bladder cancer, VPA inhibits growth of tumor xenografts [89]. In prostate cancer, VPA induces apoptosis in androgen-dependent and independent cell lines [90], and a growth inhibitory effect was also observed in xenograft models [90, 91]. For colon cancer, VPA significantly induces apoptosis in some cell lines which express APC [92], with similar results observed in primary colon cancer cells [93]. For breast cancer, VPA inhibits growth of cell lines independent of estrogen receptors [94, 95], potentiates the action of Tamoxifen, Raloxifen, Fulvestran, and Letrozol, and induces tumor regression in xenograft. Surprisingly, combined treatment with VPA and tamoxifen inhibits Ishikawa adenocarcinoma cells, which normally proliferate in response to tamoxifen [96]. In hepatocarcinoma cells, VPA increases cell death in cell lines and primary cancerous cells through the induction of TRAIL in TRAIL-sensitive cells (Figure 2), and through c-FLIP inhibition in TRAIL-resistant cells [97]. Treatment of neuroblastoma cells with VPA inhibits growth and induces neural differentiation [98]; in xenograft, VPA inhibits tumor growth by itself, but when associated with IFN-alpha can induce complete cure (33% of tested animals) [99]. VPA induces cell differentiation and adhesiveness in glioma cells [100]; it potentiates the action of etoposide for the induction of apoptosis in these cancer cell types [101]. In Thyroid cancer, VPA acts upon both poorly differentiated, and anaplastic cells, by inducing proliferative and proapoptotic effects through inhibition of BCL-2 and BCL-xl, and induction of Bax [102].

A dose escalating phase I clinical trial, realized in 2007, targeted refractory advanced solid tumors in 26 pretreated patients and gave the first indication of the effect of VPA treatment maximum tolerated dose (MDT). Doses of up to 60 mg/kg/d for 5 consecutive days were well tolerated and showed detectable biological activity; doses of 90 to 120 mg/kg/d corresponded to the incidence of dose-limiting toxicity (DLT), dominated mainly by neurocognitive

impairment, with grade 3 or 4 neurological side effects occurring in 8 out of 26 patients. No grade 3 or 4 hematological toxicity was observed [103].

Concerning clinical trials upon breast cancer, initial results showed that cotreatment with hydralazine and magnesium valproate exerts the proposed molecular effects of DNA demethylation, HDAC inhibition, and gene reactivation in primary tumors [104]. Recently a phase I/II study was conducted to study the effects of valproic acid in patients with breast cancer [105]. This study, which focused on the HDACi effect of VPA, was based on 44 patients with phase I cancer who had solid tumors and adequate organ function. The phase II dose expansion enrolled 15 patients with locally advanced (III), or metastatic (IV), breast cancer. Partial responses for 9 of 41 (22%) patients within the phase I cohort, and objective responses for 9 of 14 (64%) patients in the phase II cohort, demonstrated that valproic acid is clinically relevant regarding its HDAC inhibition activity in solid tumor malignancy. This study, which also investigated markers of HDACi efficacy, proposed that efficiency should be checked using peripheral blood rather than the tumor, and that the activity of HDAC2 should be targeted.

A recent phase I/II clinical trial aimed to examine the capacity of VPA to potentiate the effect of karenitecin (KTN: a topo I inhibitor) on *melanoma cells*. The previous studies in multiple melanoma cell lines, and in mouse A375 xenografts, had been conducted and showed that VPA pretreatment potentiated KTN-induced apoptosis. This clinical study, realized in patients with stage IV melanoma, with any number of prior therapies, aimed to investigate DNA cleavage, cytotoxicity, and maximum tolerated dose (MTD) induced by KTN and VPA. Encouraging results were shown for a VPA MTD of 75 mg/kg/d (1.28 mmol/L), in which 15 patients were evaluated for toxicity and efficiency; 47% (7 of 15) of patients with metastatic poor prognosis melanoma showed disease stabilization [106]. In comparison, another stage I/II clinical trial aimed to evaluate the biological activity of VPA, following cotreatment with standard chemoimmunotherapy (dacarbazine, 800 mg/m^2 plus Interferon-α) for advanced *melanoma* patients. 29 patients were eligible and started taking valproate, 18 received chemoimmunotherapy and were assessed for response. Results showed only one complete response, two partial remissions, and three disease stabilizations lasting longer than 24 weeks and triggered an increase in side effects. In conclusion, VPA treatment did not produce results superior to standard therapy in patients with advanced melanoma and induced severe side effects with grade 3 (anemia, abdominal pain, ataxia, neutropenia, thrombocytopenia, hypocalcemia, depression consciousness, neurological disorder, and urinary incontinence) and grade 4 (Dyspnea, anemia, depression consciousness, neurological disorder thrombocytopenia, and cerebral hemorrhage) toxicities [107].

The use of orally administered VPA in a clinical trial targeting castration-resistant prostate cancer (CRPC) showed that two out of ten patients had prostate-specific antigen (PSA) responses, of which only one response was durable. Weekly biomarker collections revealed PSA levels inversely correlated with total VPA levels, but no histone acetylation

was consistently observed in peripheral lymphocytes. VPA toxicity effects were grades 1 and 2 for neurologic events, and grades 1 and 2 for fatigue [108]. This study concluded that it was unlikely that the observed effects upon PSA were due to the HDACi activity of VPA, and as such oral-VPA is not recommended to treat prostate cancer.

In conclusion, VPA has been used for many years in the treatment of many neurological disorders including convulsive seizures related to epilepsy, as a mood stabilizer and in the treatment of schizophrenia. Moreover, VPA has been involved in clinical trials for several other neural disorders or diseases, such as addiction, migraine, and ALS. Accordingly, investigation of side effects will be crucial for the future use of this drug.

5. Drug's Interactions

To date a total of 606 drugs are known to interact with VPA, 12 major, 546 moderate, and 48 minor interactions (http://www.drugs.com/). The major drug interactions are with acetaminophen, aspirin/caffeine, cilastatin/imipenem, doripenem, ertapenem, lamotrigine, meropenem, propoxyphen, sodium benzoate, sodium oxybate, sodium phenylacetate, and vorinostat.

Aspirin, caffeine, and other salicylates can inhibit the clearance of valproic acid and increasing its serum-free concentration up to 4 times [109], this may help to reduce the daily dose of VPA but also increase its cytotoxicity when administered with aspirin [110]. Imipenem, Meropenem, Doripenem, Ertapenem, and Panipenem antibiotics decrease the serum concentrations of valproic acid likely by increasing the metabolism of VPA to VPA glucuronide as well as the renal clearance of VPA glucuronide and by inhibiting the intestinal absorption of VPA [111, 112]. Valproic acid has been shown to significantly increase the plasma concentrations of lamotrigine (doubling the half-life) [113–115] potentially leading to serious and life-threatening rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis, but also disabling tremors and ataxia, known as secondary effects of lamotrigine [116, 117]. Propoxyphene interaction with VPA is associated with an increasing probability of hip fracture by 60% in the elderly, presumably due to additive psychomotor impairment [118]. Moreover, as reported in several medical websites, propoxyphene could induce additive CNS- or respiratory-depressant effects and cause drug-related deaths particularly when used with VPA, in patients with emotional disturbances or addiction. Administration of valproic acid diminishes the therapeutic effects of sodium benzoate and sodium phenylacetate in the treatment of acute hyperammonemia due to deficiencies in enzymes of the urea cycle (see Side-effects chapter) [119–121]. The therapeutic action on central nervous system and respiratory of sodium oxybate (gamma-Hydroxybutyrate, GHB) can be potentially increased by other CNS-depressants which includes the VPA, but short-chain monocarboxylic acids and medium-chain fatty acids significantly inhibited in a competitive manner GHB brain-influx by 35 to 90% [122] which leads to the decrease of the effect of this

molecule. Coadministration of VPA (and other HDACi) with vorinostat (suberoylanilide hydroxamic acid, SAHA) can severely aggravate thrombocytopenia and gastrointestinal bleeding induced by the treatment with SAHA [123, 124].

6. Side Effects of VPA

Valproic acid (VPA) is generally used as a first-line anticonvulsive agent. It is currently in clinical trials for treatments in many fields, such as neurological disorders, cancer treatments and addictions, or as an antiviral complement. However, as with many antiepileptic drugs, there are a number of consequences associated with the use of VPA.

Many side effects related to clinical use of VPA have been reported in the literature. Most of them describe its mild and transient side effects on patients [125] but also its serious effects on embryonic development that results in physical and cognitive alterations. However, it is quite rarely made reference to other side effects that can cause significant disorders or even death of patients (Table 2).

6.1. Specific Mild Side Effects of VPA to Young Patients. Several mild side effects have been reported in patients treated with VPA, during or after the end of treatment. In one study, parents reported an increase in sleep duration during VPA treatment on young patients. However, this study—based upon sleep duration and its changes during, and up to 8 weeks after the end of treatment—[126] showed that after recalibration of sleep as a function of age, it was the cessation of VPA treatment that induced a decrease in sleep time. This was at a mild level for most patients, but considerable in a subgroup of children, especially the youngest. It also appears that VPA played a role in daytime sleepiness.

VPA has also been associated with weight gain and with changes in serum triglycerides, cholesterol, and fast glucose, but studies into these effects have shown only slight impacts of treatment upon weight gain in young children or teenagers [127, 128]. Body mass index scores tend to increase during the first 16 months of treatment and then tend to stabilize, resulting in an increase in the proportion of young children in the clinically overweight category from 6.9% to 16%. In older children, there was a 14% change to a higher weight category. However, the overall results showed no significant variation in the composition of fatty acids in serum.

6.2. Dermatologic Side Effects. Valproic acid can be associated with cases of stomatitis, cutaneous leukoclastic vasculitis, and psoriasiform eruption [141]. Valproic acid induced alopecia due to the telogen shedding which appears within three months of the initiation of the treatment. It induces also transient alopecia (2.6% to 12%), thinning of the hair, hair color changes, hair texture changes, and rare rashes. Alopecia is not dose related and can be prevented by treatment with zinc and selenium-containing vitamin. VPA was also implicated in Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell Syndrom) [142].

TABLE 2: *Side effects and prevalence*. List of classified side effects observed during treatment with VPA. NA: Data not available.

Mild side-effects	Prevalence
Decrease of sleep duration after the end of treatment	15 to 45 min/day [126]
Weight gain	14% change of weight class [127, 128]
Drowsiness	NA
Nausea	NA
Unsteadiness	NA
Decrease appetite	NA
Fertility and teratogenic effects	*Prevalence*
Decrease of fertility	25% [129]
Spina bifida	
Anencephaly	
Cardiac defect	3-fold increase [130–132]
Dysmorphic features	
Valproate syndrome (decrease of intrauterine growth)	
Craniofacial, skeletal, or limb defect	
Problem of communication development	NA
Autism spectrum	NA [132]
Decrease of IQ	9 points [133, 134]
Disorder or decrease of verbal intelligence	NA
Neurological side-effects	*Prevalenc*
Ischiemic stroke (if associated with MTHFR mutation: 5–22% of population)	1 case reported [135]
Enchephalopathy	NA [120]
Exacerbation of epilepsy	1 case reported [136]
Parkinsonism	1.37–5.04% [137]
Liver damages	*Prevalence*
Child hepatotoxicity	0.16% [138, 139]
Hematopoietic damages	*Prevalence*
Thrombocytopenia	
Platelet dysfunction	
Factor XIII deficiency	4% [120]
Hypofibrinogenemia	
Vitamin K dependent factor deficiency	
von Wilbrant disease	67% in children 16% in adults [120]
Aplastic anemia	9-fold increase [140]

6.3. *VPA Effects on Fertility, Pregnancy and Fetus Development.* The influence of VPA upon murine fertility, and that of the descendants, has been well reported: VPA decreases the fertility index by 25% and decreases the number of fetuses. To a large degree, these side effects can be corrected by administration of folic acid, 5-formyltetrahydrofolate (FOL), and S-adenosylmethionine (SAM) [129], indicating the effect of VPA on the folic acid cycle.

Prospective and retrospective studies demonstrate that VPA is a human teratogen, with an approximately threefold increase in major anomalies [131, 132], which is greater than that observed for other antiepileptic drugs (AEDs). Comparative studies show that while other AEDs increase the risk of malformation from 2.9 to 3.6%, the risk of major congenital malformation obtained with VPA is between 6.2 and 7.6% [143]. These disorders usually comprise spina bifida, and more rarely anencephaly, cardiac, craniofacial skeletal or limb defects, dysmorphic features, and a decrease in intrauterine growth (Valproate syndrome) [130]. Moreover, children affected by Valproate Syndrome generally present developmental or communication problems, such as autistic spectrum disorder or decreased verbal intelligence [132]. The increased rate of disorders could be linked with taking more than 1000 mg daily, or linked with polytherapy. Therefore, pregnant women treated with VPA, and without the possibility of substitution treatment, are recommended to decrease dosage by 2 to 3 daily doses, limit treatment to monotherapy and, in addition, to take folic acid and increase the frequency of ultrasonographic assessments to assess any malformations more precisely. It has been suggested that the teratogenic effects of VPA could be due to impaired methionine synthesis and DNA hypomethylation [144], as VPA induces disturbance of the folic acid cycle and subsequent synthesis of methionine [129]. It can also be due

to the increase in oxidative stress, to which the brain is more susceptible than the other fetal organs [132].

Finally, the effects of VPA may also have impact on the child's intellectual development, without description of malformation, autism syndrome, or problems in communication. Recent interesting publications aim to quantify the IQ of off-spring of women taking VPA or other AEDs during pregnancy. It follows from this study on more than 300 children, that exposure to AEDs (Lamotrigine, Phenytoin, Carbamazepine and Valproic acid) during pregnancy can impair brain development of children. This phenomenon is particularly important with VPA, causing a significant decrease in IQ by 9 points on average, irrespective of maternal IQ [133, 134]. These results show also that the decrease is dose dependant.

6.4. Neurological Side Effect of Treatment with VPA. VPA has been used for many years as an anticonvulsant and antiepileptic drug. In the recent years, it has been associated with treatment or clinical trials for other neurological disorders, such as mood disorders, schizophrenia, or attention deficit hyperactivity disorder. Due to its direct neurological action, it is not surprising to see the emergence of side effects in the same field.

One report described 19 new cases of encephalopathy in 2006 in Germany that possibly implicate valproic acid [120]. These cases are in addition to the 51 cases previously described in the literature. While it had been previously reported that these side effects were visible only in children with metabolic defects, the new results reveal that the same effects are found in adult patients. In these cases of encephalopathy, a possible direct action of VPA upon neurotransmitters has been postulated, which would explain the emergence of the pathology in the absence of liver failure or hyperammonemia [145], and in cases of hyperammonemia, VPA could inhibit the urea cycle.

Valproate-induced Parkinsonism was recently described in the literature. Tested among several EADs, the VPA has shown the greatest ability to induce Parkinsonian symptoms, increasing the population tested from 0 to 5.04% [137]. They show that the effects are reversible and can be controled by a decrease of the dose. Moreover, they also reported that the symptoms can appear from a dose of 750 ± 273.86 mg/day in long-term treatment (all patients have been taking VPA for more than 3 years). Three years earlier, Easterford et al. presented the same results, with an incidence corresponding to a 10 times increase of the symptoms, but suggesting that dopaminergic neuronal loss is not the underlying mechanism, since beta-CIT-SPECT scans showed normal results [146]. Nevertheless, short-time treatment showed also significant incidence. After one year of treatment a significant increase up to 1.37% of parkinsonism or cognitive decline (P/CD) induced by VPA was reported [147]. Finally, one patient with short-term Valproate-induced Parkinsonism (3 months) has been described in [148]. In this case, the authors hypothesized that valproic acid acts through damage of the protoplasmic astrocytes and the decrease of the number of gliofilaments.

Hyperammonia is a pathology generally associated with liver failure. In patients treated by VPA, hyperammonia was observed in the absence of liver failure [121], resulting in vomiting, ataxia, behavioral changes, lethargy, somnolence, or coma. However, it seems that the majority of VPA-induced hyperammonia cases in children are asymptomatic and can be detected only by blood tests or psychomotor speed, reaction time, and memory assessment. It should be noted that long-term hyperammonemia can induce encephalopathy.

In a recent study, VPA was involved in an acute ischemic stroke in a patient with a mutation of methylenetetrahydrofollate reductase (MTHFR) 677C/T [135]. The rate of this mutation, that varies from 5 to 22% of the population, results in a decrease in MHTFR activity from 70% to 30%, for homozygotes and heterozygotes, respectively, which induces hyperhomocysteinemia (Hcy), a possible risk factor for epilepsy and occlusive vascular disease. It had already been reported that Hcy could be exacerbated by the use of VPA, by reducing folic acid and Vitamin B12 levels. This study highlights the risks associated with VPA treatment for this pathology and recommends taking into account family epilepsy history to determine the level of Hcy, particularly in the case of long-term treatment, in order to promote patient survival.

While the effectiveness of VPA is recognized in the treatment of epilepsy, including cases of Juvenile absence epilepsy, little is known about the paradoxical effects that this molecule can have, for instance, the exacerbation of these disorders. This rare phenomenon was described in 2007 for a young patient [136].

6.5. Association between VPA and Liver Damage. For a long time, it has been shown that hepatotoxicity induced by VPA is greatest in children under 2 years old undergoing polytherapies [138, 139, 149]. The prevalence of hepatotoxicity is 1 per 618 for this age bracket and decreases to 1 per 10,100 for ages 11 to 20 years. Exposure of the liver to the VPA degradation product is the most likely explanation for cases of hepatotoxicity observed during treatment, particularly for young children. The VPA degradation product (E)-2,4-diene VPA, and two conjugation forms with glutathione as N-acetylcystein (NAC) conjugated, NAC1 and NAC2 for excretion in urine, seem to be the main factors causing the disease [150]. A statistical study, conducted in 2003 [151], on groups of young patients treated with VPA in mono- or polytherapy type A or B, shows a clear correlation between age, dose, and quantity of conjugate found in patient's urine, with an increased excretion with decreasing age, and a pronounced effect between 0 and 7.5 years. This study also shows the lack of effect of type A polytherapy (non-P450-enzyme inducer), in comparison with the monotherapies. However, type B polytherapy (P450-enzyme inducer), which increases the metabolism of VPA, and thus increases its clearance, induces a significant increase in the excretion of NAC.

There is a correlation between ages, treatment, and amount of conjugate excreted, the latter reflecting exposure

of the liver to VPA degradation products. This correlation may be predictive, as it is possible, using gas chromatography coupled with mass spectrometry, to determine dosage quantities precisely: using these two indices could be the most promising indicator for prediction of this side effect.

6.6. VPA and Hematological Disorders. Coagulopathies were described in children treated with VPA [123]. More than 4% of children treated with VPA demonstrate this pathology, but this is likely to be a significant underestimate. Symptoms found in this disorder are thrombocytopenia, platelet dysfunction, Von Wilbrant disease, Factor XIII deficiency, hypofibrinogenemia, and vitamin K-dependent factor deficiency.

Two hypotheses could explain the thrombopenia and platelet dysfunction. The first is that VPA has a direct toxicity on bone marrow, which decreases production of neutrophilic and erythroic marrow. The second hypothesis involves the inclusion of VPA into the platelet membrane (structural and chemical similarity with the fatty acids of cell membranes). This membrane modification could cause autoimmunity, due to the production of immunogobin M antibody directed against circulating thrombocytes, but this modification could also cause simple alteration of membrane properties, which could explain the observation of thrombocytopenia without decrease in platelet number. VPA-induced von-Willebrand disease has been reported as having a high prevalence (around 67% in children during VPA treatment, and 16% for adult patients). The mechanism inducing the pathology has not been elucidated, but vWF is downregulated, without dose effect correlation, and the pathology is reversible following treatment, or can be corrected by desmopressin. Vitamin K-dependent coagulopathy induced by VPA could imply a competitive mechanism between the two molecules for binding sites in plasma—as unbound Vitamin K has a shorter half-life—or in one of the many metabolic pathways shared by these molecules. VPA-associated hypofibrinogenemia does not appear to have a major influence in coagulopathy but is always associated with a more important pathology, as described previously, and is probably involved in an as yet unknown step in hepatic synthesis. VPA-associated factor XIII deficiency has been described in a few patients, with the involvement of VPA not in doubt, because of recovery after treatment and the rarity of double mutation. No explanation has yet been advanced to explain the phenomenon, but the influence of VPA in the synthesis of other liver factors has been reported on several occasions.

A second side effect of blood type, after the use of VPA (or other antiepileptic drugs such as carbamazepine and phenytoin), is the development of aplastic anemia [140], for which prevalence appears to be increased by more than 9 times. Just as it has been reported for hepatotoxicity, it appears that aplastic anemia has a higher prevalence during polytherapy. However, given that aplastic anemia is a malfunction of hematopoietic stem cells, inducing a break in the production of erythrocytes, the results reported in this study contradict those which suggest VPA as a potent activator of erythropoiesis in epileptic patients [152]. This study of 30 young patients treated for more than 3 months with VPA anticonvulsive doses shows an increase of the expression of fetal hemoglobin, with dose-dependent stimulation.

7. Conclusion

VPA is a molecule exhibiting a wide range of effects upon various tissues, pathologies, and patient profiles. This molecule is capable of altering the expression of more than 20% of the transcriptome in a tissue-dependent manner. Therefore, it is currently very difficult to anticipate all the effects that may occur during treatments in mono- or polytherapies.

On one hand, VPA has been used for many years in the treatment of convulsive seizures related to epilepsy, as a mood stabilizer and in the treatment of schizophrenia. More recently, VPA has been involved in clinical trials for several other neural disorders or diseases, such as addiction, migraine, and ALS. Its efficiency in the treatment of cerebral alterations is the most described.

On the other hand, modifying the expression of oncogenes or anti-oncogenes could be a profitable strategy in the fight against various forms of cancer. In this regard, VPA appears to have some undeniable qualities, such as the induction of cell death (mainly by apoptosis) and differentiation, and the inhibition of proliferation. Interestingly, it seems that healthy cells are much less sensitive to these properties.

In light of all these observations and considering the increase of clinical trials involving VPA, it is highly likely that this molecule will be used in many therapies in the near future. Nevertheless, numerous publications related to therapeutic effects of VPA also mention possible side effects associated with treatments. Thus a variety of side effects, including coagulopathies, aplastic anemia, hepatotoxicity, and teratogenic effects have been reported. Some preexisting pathologies such as hyperhomocysteinemia or coagulopathy and pregnancy contraindicate the use of VPA as a treatment.

Balancing therapeutic potentialities with serious side effects observed following use of VPA to favor the advantageous effects will no doubt prove to be a challenging and complex issue for clinical management.

Acknowledgments

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