Chapter 3
Historical Overview on Baclofen, the Only $GABA_B$ Receptor Agonist Approved and Available for Clinical Use

Mauro A. M. Carai

Abstract Baclofen was synthesized in 1962 as a component of a group of ß-aryl-halogenated GABA derivatives capable of crossing the blood-brain barrier and, thus, exerting inhibitory effects on the central nervous system. At that time, the role of GABA as a neurotransmitter had not been fully discovered, and nothing was known about its receptors. The clinical development of baclofen was based on its muscle-relaxant effects. Ten years after its synthesis, baclofen was registered in Europe as Lioresal®; registration in the United States occurred in 1977. Over the following decade, baclofen became the drug of choice for the treatment of spasticity and muscle spasms. Anecdotal reports from patients taking baclofen for its approved indications led to the identification of additional, possible uses (often supported by accumulating findings on the central and peripheral functions of GABA neurotransmission). Among these new indications, it is worth mentioning the treatment of substance use disorder, which actually represents the sole, recent advancement in terms of authorizations. Since the early 1980s, baclofen actions at specific GABA receptors (named $GABA_B$) were discovered. It is now hoped that future research will focus on (i) possible new clinical applications of baclofen and (ii) new $GABA_B$ receptor agonists, including those naturally occurring, that would hopefully come alongside baclofen and possibly extend its therapeutic prospects.

Keywords GABA derivatives · Baclofen · Lioresal® · Therapeutic use · Off-label use · Clinical development

3.1 From GABA to Baclofen

Since the eighteenth century, at a time when methodological and scientific findings were starting to lay the groundwork for the future development of pharmacology, plant-derived alkaloids have repeatedly been associated with novel discoveries of

M. A. M. Carai (✉)
Cagliari Pharmacological Research, Cagliari, CA, Italy

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major importance (see Holmstedt and Liljestrand 1981). Indeed, relevant insight into the mechanism of action of baclofen was unequivocally linked to one such alkaloid. In 1932, Richard H.F. Manske, an outstanding Canadian chemist who provided a fundamental contribution to the isolation and characterization of numerous alkaloids, published the findings of his studies on a series of alkaloids extracted from *Dicentra cucullaria* (Manske 1932). At the time, γ-aminobutyric acid (GABA) was already well known, with the synthesis of the compound being described for the first time in 1883 (Schotten 1883), followed by the demonstration in 1910 of the presence of GABA in biological tissues (see Roberts and Frankel 1950). However, the presence of GABA in the central nervous system (CNS) was only identified in the 1950s (Roberts and Frankel 1950), and it was not until 1959 that a study was published affirming that "*These observations on the effects of GABA on the guinea-pig ileum have been confirmed in the present series of experiments; however, no inhibitory effect of GABA on induced contractions of rabbit ileum has been detected. Factor I has been found to have effects qualitatively similar to GABA*" (Florey and McLennan 1959). Factor I was indeed an inhibitory factor extracted from the brain, and this important finding led scientists to hypothesize the likely role of GABA as a neurotransmitter (Florey and McLennan 1959). However, despite these observations, a widespread debate focused on whether or not GABA acted as a neurotransmitter was ongoing until 1967. In the same year, a study entitled, "The action of gamma-aminobutyric acid on cortical neurons" was published, demonstrating in a series of convincing electrophysiology experiments that GABA was indeed an inhibitory neurotransmitter, with the authors stating, "*When γ-aminobutyric acid is applied to single cortical neurons, it causes changes in membrane potential and conductance that are similar to the effects of synaptic inhibition. It is therefore concluded that this normal constituent of the brain could be the physiological transmitter at inhibitory synapses in the cerebral cortex*" (Krnjević and Schwartz 1967). It was at this point that bicuculline, one of the alkaloids isolated and characterized by Manske, first appeared on the scene; no therapeutic indications had been proposed for this alkaloid, and indeed, this remains the case today, although the role of bicuculline as a GABA antagonist gained rapid consensus. Four detailed reports were published in 1970 demonstrating the antagonistic activity of bicuculline (Curtis et al. 1970a, b, c; Godfraind et al. 1970) and indicating this organic compound as a powerful tool for use in studying GABA-mediated inhibitory transmission. One of these studies successfully determined that bicuculline antagonism of GABA effects was not, in turn, inhibited by strychnine (Eccles 1969; Curtis et al. 1970c), thus helping to discern between the effects of GABA and those produced by glycine when the latter acted as a neurotransmitter. This paved the way for a period of rapid advancement in the knowledge of GABA-mediated transmission and GABA receptors and led to GABA being deemed responsible for 40% of inhibitory synaptic transmission in the CNS. Moreover, further studies clarified how the action of GABA increased neuronal membrane permeability to chloride. Benzodiazepines, an emerging class of novel hypno-sedative drugs, were found to act by potentiating the effects of GABA-mediated transmission (Haefely et al. 1975).

During the 1970s, in the midst of this period of increased awareness, several researchers observed how neurons of the sympathetic or dorsal root ganglia were implicated in producing GABA effects. Indeed, although no significant differences were present between the CNS and the peripheral nervous system (PNS), with the effects of GABA invariably mediated by an increased influx of Cl^- ions into intracellular compartments, the potential remained markedly lower in sympathetic neurons compared to the CNS, with values of −42 mV and −75 mV, respectively (see Bowery 2010). Additional studies aimed at clarifying this discrepancy led to the differentiation of GABA receptors. In a series of key experiments performed in rat heart atria, GABA effects were found to underlie a reduction in evoked release of tritiated noradrenaline; surprisingly, although not antagonized by bicuculline, this effect was substantially, and in a stereospecific manner, reproduced by β-chlorophenyl-GABA or baclofen (Fig. 3.1), thus persuading Norman G. Bowery and colleagues that they had identified a new GABA receptor (Bowery et al. 1979, 1980; see also Chap. 15 of this volume). These findings were subsequently followed by a series of accomplished studies resulting in the definition of GABA type-A ($GABA_A$) and type-B ($GABA_B$) receptors, which, in turn, led to the discovery and fundamental understanding of their mechanisms of action and composition (see Bowery 2010, 2016).

At this point, however, we should take a step back in an attempt to grasp how Bowery and his collaborators were able to identify an agonist for a receptor that had yet to be discovered. Based on the history of pharmacology, this question may appear rather banal, as it is indeed an acknowledged fact that man has invariably succeeded in identifying naturally-occurring substances prior to the identification, at a later date, of synthetic compounds, with mechanisms of action only being revealed in more recent decades, following thousands of years of therapeutic or recreational use (see Holmstedt and Liljestrand 1981; Efron et al. 1967). The history of baclofen dates back to the early 1960s, when, in anticipation of clarification of the neurotransmitter role played by GABA, the race had begun to obtain derivatives capable of penetrating the CNS, i.e., molecules capable of crossing the blood-brain barrier (BBB) and thus exerting a therapeutic action on the CNS. One means of augmenting the lipophilicity of GABA lay in the potential insertion of lipophilic substituents into the GABA molecule, thus giving rise to a dedicated research program led by a group of researchers at Ciba in Basel,[1] and baclofen (initially known as Ciba 34647-BA) was subsequently synthesized in September 1962. The research group involved in these discoveries was led by Heinrich Keberle, an investigator who had worked for more than 30 years for the company that would become Ciba Geigy in 1970; Johann Werner Faigle and Max Wilhelm were also members of

[1] Ciba AG (Chemische Industrie Basel) was a Swiss chemical and pharmaceutical company established in 1859. Following the merger of Ciba AG and J.R. Geigy SA in 1970, Ciba Geigy was formed.

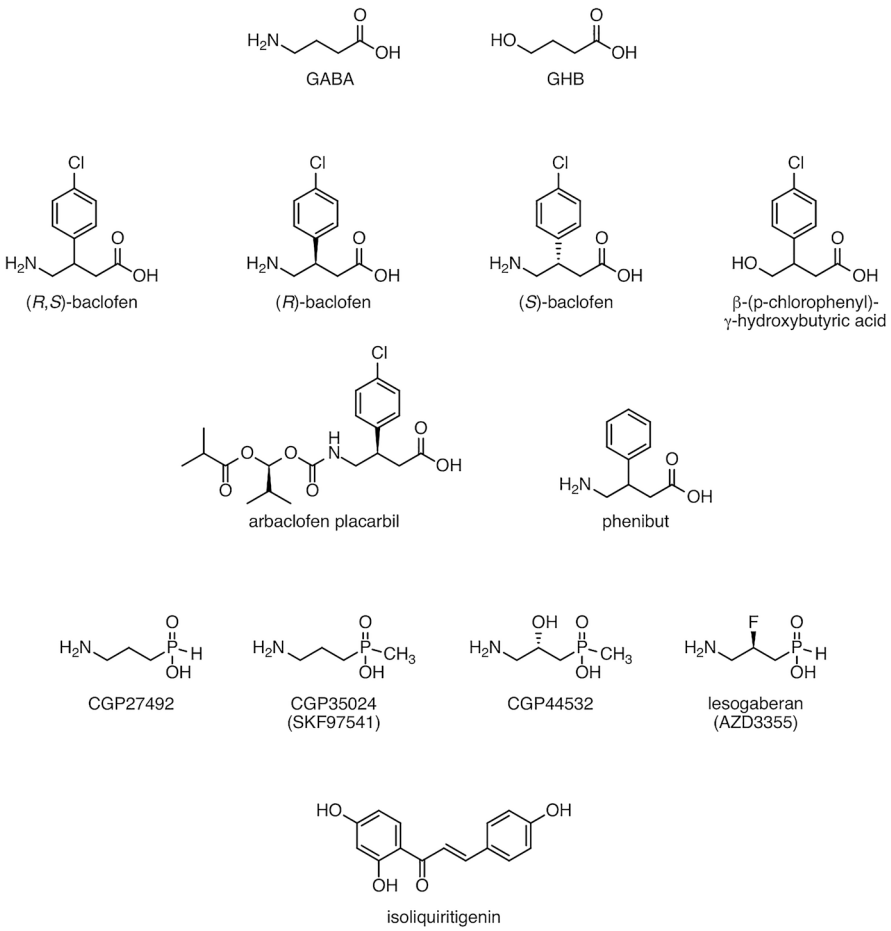
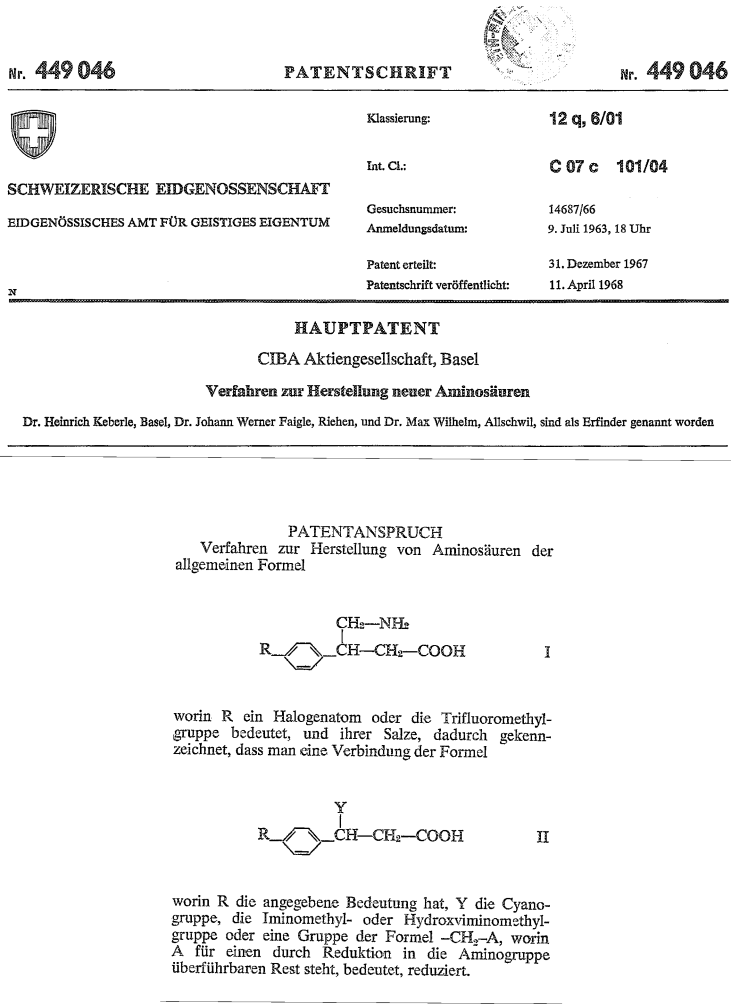


Fig. 3.1 Chemical structure of GABA, baclofen (including enantiomers, pro-drugs, metabolites, and analogs), γ-hydroxybutyric acid (GHB), and $GABA_B$ receptor agonists

Keberle's lab and were included on the list of authors for a patent deposited by Ciba on July 9, 1963, entitled *Verfahren zur Herstellung neuer Aminosäuren* "Process for producing new amino acids"[2] (Fig. 3.2) (Espacenet 2024).

[2] Heinrich Keberle had come up with the idea of synthesizing a GABA analog featuring the characteristics cited following his participation in a conference organized by Wilhelm Feldberg at the Royal Society in London (see Bowery 2016). As the history of the twentieth century raged, the fractures started to appear: Feldberg was a German pharmacologist of Jewish origin who was banished from the Physiological Institute in Berlin in 1933 and subsequently admitted, in 1934, to the National Institute for Medical Research, situated on the outskirts of London, where he embarked on a close collaboration with Henry Hallett Dale, a distinguished twentieth-century British pharmacologist who, in 1936, shared the Nobel prize with Otto Loewi for their research on the role of acetylcholine in neurotransmission (Feldberg 1969).



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HAUPTPATENT

CIBA Aktiengesellschaft, Basel

Verfahren zur Herstellung neuer Aminosäuren

Dr. Heinrich Keberle, Basel, Dr. Johann Werner Faigle, Riehen, und Dr. Max Wilhelm, Allschwil, sind als Erfinder genannt worden

PATENTANSPRUCH

Verfahren zur Herstellung von Aminosäuren der allgemeinen Formel

I

worin R ein Halogenatom oder die Trifluoromethylgruppe bedeutet, und ihrer Salze, dadurch gekennzeichnet, dass man eine Verbindung der Formel

II

worin R die angegebene Bedeutung hat, Y die Cyanogruppe, die Iminomethyl- oder Hydroxviminomethylgruppe oder eine Gruppe der Formel $-CH_2-A$, worin A für einen durch Reduktion in die Aminogruppe überführbaren Rest steht, bedeutet, reduziert.

Fig. 3.2 Title page and claims of Swiss patent no. 449046. Date of application filling: July 9, 1963, 18:00; date of patent grant: December 31, 1967; date of patent publication: April 11, 1968. Claims provide as follows: "*Process for producing amino acids of the general formula I, where R means a halogen atom or the trifluoromethyl group, and their salts, characterized in that one is a compound of the formula II, where R has the meaning given, Y is the cyano group, the iminomethyl or hydroxyiminomethyl group or a group of the formula -CH_2-A, where A stands for a residue that can be converted into the amino group by reduction*"

The Basel chemists had successfully met their objective of improving, at least in part, GABA lipophilicity; GABA has an estimated value of log of partition coefficient (logP) of −3.17, while baclofen has a logP of 1.3 (PubChem 2024a, b). Consequently, the lipophilicity of baclofen was not sufficient to cross the BBB by means of passive diffusion, and it was subsequently reported that this occurred by means of a carrier-mediated transport system (van Bree et al. 1988). In 1972, Keberle and Faigle published partial data obtained from their baclofen studies

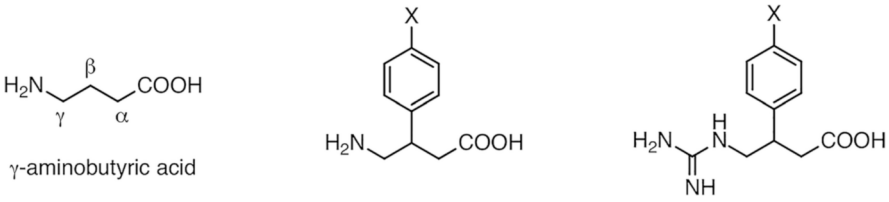

Fig. 3.3 Chemical structure of some of the GABA-related compounds, including baclofen, tested by Faigle and Keberle (1972) for biological activity. X stands for a generic substituent

(Faigle and Keberle 1972), highlighting how only GABA derivatives featuring an aromatic ring in the β position of the amino acid displayed "central inhibitory effects," with the γ-guanidine GABA analog representing the only other active compound (Fig. 3.3). Moreover, Keberle and Faigle were in charge of setting up pioneering pharmacokinetic studies in animals and humans in which, further to establishing the ready absorption of baclofen in the gastrointestinal tract, they demonstrated how the compound was excreted largely unchanged, identifying β-(4-chlorophenyl)-γ-hydroxybutyric acid (Fig. 3.1) as one of the main metabolites (Faigle and Keberle 1972).

However, the limited ability of baclofen to cross the BBB was not the only problem; indeed, although baclofen had been developed as an anti-convulsant drug, the studies performed failed to yield promising results. Unfortunately, the findings of experimental in vivo studies carried out by Ciba were never published, although the highly complex role of the $GABA_B$ receptor in epilepsy is now widely acknowledged. Put simplistically, as a $GABA_B$ receptor agonist, baclofen elicits the onset of typical and atypical absence seizures, which, on the contrary, are prevented by $GABA_B$ receptor antagonists. However, to cite a mere example, in animal models of focal seizures, low doses of baclofen, i.e., 1 mg/kg, lower the seizure threshold, while doses exceeding 10 mg/kg raise the threshold (see Joshi et al. 2016). Accordingly, efforts to introduce baclofen as a therapeutic option in this field were largely thwarted. However, while investigating potential therapeutic applications for baclofen, scientists became aware of its muscle-relaxant properties, placing increased focus on this aspect during the drug development process.

3.2 Clinical Use of Baclofen

Long before Bowery and co-workers identified the $GABA_B$ receptors and the specific actions of baclofen on these receptors, baclofen was marketed as a drug by Ciba Geigy under the brand name Lioresal® (Fig. 3.4). Wolfgang Froestl refers to the marketing of Lioresal® occurring in 1972 (see Froestl 2010), while Hudgson and Weightman (1971) refer to Lioresal® being introduced in 1966.

The first clinical studies published on the use of baclofen in the treatment of spasticity were performed by Bergamini and co-workers in 1966 (Bergamini et al.

Fig. 3.4 Lioresal® on sale in Spain in the 1970s. (From http://www.ub.edu/pharmakoteka/node/27349)

1966) and Birkmayer and coworkers in 1967 (Birkmayer et al. 1967); these preliminary studies provided proof of the efficacy of baclofen in regulating spasticity, particularly in the context of spinal cord lesions. In 1971, in the wake of a pilot study conducted in six patients affected by severe spasticity of the lower limbs induced by multiple sclerosis or as *sequelae* of previous surgery, Hudgson and Weightman (1971) published the findings of a double-blind, placebo-controlled, cross-over trial conducted on 23 patients affected by lower limb spasticity as a result of spinal cord disease, although caused by a wider range of neurological disorders compared to previous studies. At the time, the sole option available for the treatment of spasticity resulting from spinal cord disorders or other neurological lesions was neurolysis, achieved using intrathecal injections of phenol or oral administration of the benzodiazepines, chlordiazepoxide, and diazepam, at the time considered the most effective drugs in the treatment of spasticity. However, the excess sedation caused by these drugs when administered at the doses required to treat spasticity was well-known. Hudgson and Weightman (1971) treated patients with 10 mg of baclofen t.i.d. or placebo for a period of 10 days, followed by a 7-day washout period, subsequently moving each patient to the opposite arm of the trial. The results obtained demonstrated the significantly higher efficacy of baclofen over placebo in a comparison of mean changes in spasticity (Table 3.1). No major side effects were observed, including drowsiness (Table 3.1). Over the next 2 years (1972–1973), baclofen was granted authorization in Europe under the brand name Lioresal® for use in the treatment of spasticity and muscle spasms caused by a range of neurological disorders, followed in 1977 by US authorization (Agenzia Italiana del Farmaco 2024; Food and Drug Administration 2024).

In a similar time frame, the structure of baclofen was solved as comprising two enantiomers, R(−)baclofen and S(+)baclofen (Fig. 3.1) by a researcher at Ciba Geigy, William Bencze. Isomer studies revealed the stereospecificity of baclofen, with its major effects being attributed to R(−)baclofen (see Froestl 2010). No evidence had however been provided to confirm that baclofen was a GABA-mimetic

Table 3.1 Beneficial effect of treatment with baclofen on spasticity and episodes of side effects

Improvement on baclofen					
N. of patients	Mean spasticity score		Mean improvement	SEM improvement (within patients)	*P* value
	Before baclofen	After baclofen			
23	3.74	2.30	1.44	0.230	<0.001
The mean improvement of 1.44 in patients while taking the drug is highly significant					

Improvement on placebo					
N. of patients	Mean spasticity score		Mean improvement	SEM improvement (within patients)	*P* value
	Before placebo	After placebo			
23	3.65	3.11	0.54	0.231	<0.05
The mean improvement of 0.54 in patients while taking the placebo is statistically significant at the 5% level					

	Side effects experienced by patients during trials	
	N. of patients on	
	Baclofen	Placebo
Nausea	3	1
Transient vertigo	1	–
Blurring of vision	–	1
Upper respiratory tract infection	–	1
Supraorbital pain	1	–
Sleepiness	1	–
	6	**3**

Adapted from Hudgson and Weightman (1971) with permission from The British Medical Journal
Spasticity was arbitrarily graded from 0 (normal) to 4 according to clinical evaluation. Patients were randomly allocated to placebo or baclofen (10 mg thrice daily for 10 days) under a crossover design with a 7-day washout period

drug, despite marketing authorization being granted for the compound in the 1970s as a "GABA-related drug" (see Bowery and Smart 2006).

As the use of baclofen became more widespread, limitations of the drug became evident, highlighting how, despite its rapid absorption in the upper small intestine, with a bioavailability of 75–85% and a half-life of 2–6 h (see Kent et al. 2020; see also Chap. 7 of this volume), the relatively poor ability of baclofen to cross the BBB implied a need for repeated doses and, particularly, the use of higher doses to achieve a therapeutic effect in specific patient populations, resulting in the onset of side effects including drowsiness, lethargy, convulsions, nausea, vomiting, hypotension, and respiratory depression, thus affecting baclofen manageability in these patients. These problems were, however, overcome following the introduction of the intrathecal (IT) baclofen administration. The first studies in this regard were performed by Penn and Kroin (1984), who highlighted how this new route of administration facilitated the delivery of baclofen to its sites of action within the CNS, thus yielding concentrations of the drug in cerebrospinal fluid (CSF) that would have been unachievable via an oral route of baclofen administration (see Chaps. 4

and 7 of this volume). IT baclofen at doses of 12–400 μg per day was more effective than oral treatment in restoring normal muscle tone and eliminating spontaneous spasms (Penn and Kroin 1985). Froestl (2010) reported how intrathecal doses of 600 μg baclofen produced higher CSF concentrations compared to those obtained following a 100-mg oral dose. Moreover, in addition to increased efficacy, this route of administration also proved beneficial in markedly reducing side effects typically associated with high doses of oral baclofen (see Bowery 2010; Froestl 2010). However, the use of IT baclofen unraveled a series of issues, present to a lower degree also with oral treatment, including the risk of potentially fatal overdose, generally linked to pump malfunction, and the onset of withdrawal syndrome on abrupt discontinuation of intrathecal treatment linked to pump malfunction or recharging errors (see Romito et al. 2021; see also Chap. 7 of this volume).

Almost 10 years after the introduction of baclofen in clinical practice, Bowery and co-workers made their crucial discoveries relating to the $GABA_B$ receptor, which revealed the mechanism of action of baclofen. From that time onward, the availability of radioactives proved to be a formidable tool, facilitating in-depth studies of the $GABA_B$ receptor and its distribution. In this regard, Bowery mentioned how he had approached Helmut Bittiger at Ciba Geigy to enquire into the possibility of receiving tritiated baclofen for use in receptor binding studies. One year later, Bittiger supplied the ^{3}H-baclofen, alerting Bowery to the fact that his group had failed to elucidate the binding site and attaching a detailed description of the experiments undertaken. Bowery, together with his close collaborator, David R. Hill, focused intensely on the buffer solution used by Bittiger and co-workers: a TRIS-containing solution that was widely used at the time in radio-receptor binding assays. Bowery and Hill's instincts led them to replace the latter with saline in a solution using Kreb's solution instead of TRIS as a buffer, resulting in the observation of saturable binding characterizing bicuculline-insensitive $GABA_B$ sites, in line with the hypothesis acknowledging the involvement of alkaloids in all pharmacological discoveries (Hill and Bowery 1981; see Bowery 2016).

Baclofen today plays a major role in the treatment of conditions relating to traditional indications for the drug, including spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity; baclofen may also be of some value in patients with spinal cord injuries and other spinal cord diseases. More widely, the drug may be indicated in the treatment of spastic hypertonia of the striated muscles in multiple sclerosis and spastic muscular hypertonia in spinal cord disorders of infectious, degenerative, traumatic, neoplastic, or unknown origin, i.e., spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, spinal cord compression, and spastic hypertonia of cerebral origin, particularly in cases of infantile encephalopathy, following cerebral vasculopathy, or associated with neoplastic or degenerative cerebellar disorders. In children, baclofen is indicated in the symptomatic treatment of cerebral spasticity in patients between the ages of 0 and <18 years, particularly when caused by infantile cerebral palsy, subsequent to cerebrovascular injury, or in the presence of neoplastic or degenerative cerebellar disorders (see Chap. 4 of this volume). Baclofen is also indicated in

the symptomatic treatment of muscle spasms manifested in the course of spinal cord disorders of infectious, degenerative, traumatic, neoplastic, or unknown origin, such as multiple sclerosis, spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and spinal cord compression (Agenzia Italiana del Farmaco 2024; Food and Drug Administration 2024).

3.3 Baclofen Between Off-Label Use and New Indications

A short deliberation into a series of clinical off-label or experimental uses put forward for baclofen over the 40-year period since its first introduction as a therapeutic option, although failing to obtain marketing authorization, may be of interest.

3.3.1 Bronchospasm and Cough

Several studies have suggested that the presence of $GABA_B$ receptors in the CNS and PNS, as well as in the lungs, may lay the foundation for the use of $GABA_B$ receptor agonists in the regulation of cough and bronchospasm. Recent studies conducted with baclofen and lesogaberan (Fig. 3.1) have yielded positive findings in support of these hypotheses (see Chapman et al. 1993; Prakash 2009; Badri et al. 2021; see also Chap. 5 of this volume).

3.3.2 Stiff-man Syndrome

Since 1980, the ability of oral or intrathecal administration of baclofen to produce a marked therapeutic effect in patients affected by this rare neurological syndrome, the main characteristic of which is progressive muscle rigidity, has been well known (Whelan 1980; Geffen and Chiang 2019).

3.3.3 Chronic Hiccup

A rare condition resulting in potentially severe consequences, including inevitable weight loss and lack of sleep, the etiology of the disorder remains unknown, although it is frequently associated with other severe pathological conditions. Routine treatments include metoclopramide and chlorpromazine, although these are not always effective, with the use of baclofen over the last 30 years yielding satisfactory results (see Grant et al. 1991; Launois et al. 1993; Polito and Fellows 2017).

3.3.4 Tetanus

Nowadays, a rare condition is characterized, in addition to other symptoms, by muscle rigidity and reflex spasms. Initial observations relating to the use of intrathecal baclofen date back 40 years, with baclofen remaining one of the main therapeutic options in the treatment of tetanus (Müller et al. 1986; see Rodrigo et al. 2014).

3.3.5 Charcot-Marie-Tooth Disease, Type 1A

A rare inherited neuropathy is characterized by abnormal Schwann cell differentiation, which produces a cascade of events resulting in neuronal and, subsequently, muscle lesions. Several clinical studies have demonstrated the efficacy of baclofen, in combination with naltrexone hydrochloride and D-sorbitol, in reducing myelin defects typically manifested in this disease (Attarian et al. 2014). Since 2014, the above combination of drugs has been given orphan designation by the European Medicines Agency (EMA) (European Medicines Agency 2024). However, no official marketing authorization has yet been granted.

3.3.6 Pain

Numerous bodies of evidence confirm the analgesic effect of baclofen, supported by the discovery of the siting of $GABA_B$ receptors along pain pathways. The analgesic action of baclofen is generally thought to be elicited by an inhibitory action, largely at the spinal level, on synaptic release of L-glutamate, tachykinin, substance P, and calcitonin gene-related peptide (CGRP) (see Enna and McCarson 2016).

3.3.7 Trigeminal Neuralgia

To delve further into the analgesic effect of baclofen, in 1980, Fromm and coworkers published the findings of a study conducted to evaluate the effect of baclofen on trigeminal neuralgia. This pilot study included 14 patients who received baclofen at doses of 60–80 mg/day, reporting satisfactory results and relief from paroxysmal episodes of *tic douloureux* in two-thirds of patients (Fromm et al. 1980). Subsequently, the same group of clinical researchers demonstrated a more than five-fold higher potency of the baclofen (R)-isomer compared to racemic baclofen in 9 out of 15 patients affected by trigeminal neuralgia (Fromm and Terrence 1987). Baclofen still today represents a crucial second-line drug for use in the treatment of trigeminal neuralgia in patients who fail to respond to carbamazepine and oxcarbazepine; in these cases, baclofen may be administered alone or in combination with carbamazepine, lamotrigine, or gabapentin (see Rana et al. 2023).

3.3.8 Migraine

The use of baclofen in the treatment of migraine is also worthy of mention. The first clinical study, conducted on 44 patients affected by migraine with and without *aura*, was performed in 1999 with administration of baclofen at doses ranging from 15 to 40 mg t.i.d. for a period of 12 weeks (Hering-Hanit 1999). Treatment efficacy was assessed based on headache frequency and severity, with results confirming the effectiveness of baclofen in more than 80% of patients enrolled in the study.

3.3.9 Cluster Headache

A few years later, in the year 2000, baclofen yielded interesting results in a study performed to investigate a severe, and relatively rare, condition known as cluster headache; indeed, when administered at fairly low doses (5–10 mg t.i.d.), baclofen was able to successfully prevent attacks in two-thirds of patients after 1 week of treatment (Hering-Hanit and Gadoth 2000). Baclofen is currently used as a second-line option when treatment with sumatriptan injection or oxygen inhalation, or preventative treatment with verapamil is not effective (Ashkenazi and Schwedt 2011).

3.3.10 Unstable Bladder Syndrome and Overactive Bladder

Baclofen was suggested as a therapeutic option for use in the treatment of unstable bladder syndrome and overactive bladder. The first clinical study was carried out by Taylor and Bates prior to the discovery of the $GABA_B$ receptor in 40 patients treated with a 5-mg dose of the drug. The authors reported how baclofen produced a significant improvement in all parameters assessed: degree of incontinence and frequency of nocturnal and daytime urination (Taylor and Bates 1979). Other studies were performed on patients affected by hyperactive bladder, with numerous observations reporting an improvement in bladder function in patients treated with IT baclofen (Chin et al. 2012; Abboud et al. 2017; Konstantinidis et al. 2022).

3.3.11 Gastroesophageal Reflux Disease

The premise for these studies was based on observations relating to the effect of baclofen on cough, together with those produced by transient lower esophageal sphincter relaxation (TLOSR). The pioneer of these studies was Anders Lehmann, a group leader at AstraZeneca and author of a detailed description of the use of $GABA_B$ receptor agonists in gastroesophageal reflux disease (GERD) (see Lehmann

et al. 2016; see also Chap. 5 of this volume). Preliminary findings were published in two separate studies in 1999, demonstrating the ability of baclofen and the other $GABA_B$ receptor agonists, CGP44532 and SKF97541, to reduce TLOSR in different animal models of GERD (Blackshaw et al. 1999; Lehmann et al. 1999). The following year, the first human study was conducted on healthy volunteers, indicating how single administration of a 40-mg dose of baclofen represented an alternative therapeutic option in the treatment of GERD (Lidums et al. 2000). A relatively ample body of literature supports the use of baclofen in patients affected by GERD, particularly in the presence of concomitant conditions such as alcohol use disorder (AUD), non-acid reflux, and obesity (see Arabpour et al. 2023). Other $GABA_B$ receptor agonists tested in the treatment of GERD include the prodrug of R(−) baclofen, arbaclofen placarbil (Fig. 3.1) (Gerson et al. 2010), and lesogaberan, the latter acting mainly at a peripheral level (Lehmann et al. 2009; Boeckxstaens et al. 2010; Miner Jr et al. 2014; see also Chap. 4 of this volume).

3.3.12 Fragile X Syndrome and Autism Spectrum Disorder

These two conditions are more closely linked to CNS disorders, for which baclofen has been put forward as a therapeutic option (see Haile 2016). Fragile X syndrome (FXS) constitutes the major genetic cause of autism, with the majority of individuals affected by FXS meeting criteria established for a diagnosis of autism or autism spectrum disorder (ASD). Based on anecdotal observations reporting an improvement in these conditions following the administration of baclofen to treat spasticity and the consideration that $GABA_B$ receptor agonists possess the ability to control overactivation of brain regions involved in regulating behavior, a series of clinical trials using arbaclofen was set up from 2012 onward. These clinical trials, which saw the recruitment of hundreds of patients in double-blind, randomized, and placebo-controlled studies, many of which were sponsored by the company Seaside Therapeutics, seemingly failed to show any effect of arbaclofen on main endpoints but yielded interesting cues as to its efficacy on secondary endpoints (Erickson et al. 2014; Berry-Kravis et al. 2012, 2017). The findings of another clinical trial set up in 2021, as a multi-site, double-blind, parallel group, Phase II randomized clinical trial on 130 children and adolescents are expected forthwith (Parellada et al. 2021).

3.3.13 Panic Attacks

The findings of a double-blind, placebo-controlled, crossover trial were published in 1989, reporting the effects obtained by a 30-mg dose of baclofen once daily for 4 weeks; baclofen was found to be more effective than placebo in preventing panic attacks and improving scores obtained at a series of rating scales used to measure anxiety (Breslow et al. 1989).

3.3.14 Post-Traumatic Stress Disorder

In a small pilot study published in 2003, 14 patients affected by chronic, combat-related post-traumatic stress disorder (PTSD) were treated with doses of baclofen up to 80 mg daily. The authors reported how, compared to baseline values, following 8-week treatment with baclofen, lower scores were obtained at the Clinician-Administered PTSD Scale (CAPS) (Drake et al. 2003). In another double-blind clinical trial, a daily dose of 40 mg of baclofen was combined with either citalopram or placebo over an 8-week treatment period (Manteghi et al. 2014). This study likewise observed a significant improvement in the CAPS score and score obtained at the Global Assessment of Functioning with regard to depression and anxiety compared to placebo.

3.3.15 Anxiety

Preclinical and clinical studies have implicated $GABA_B$ receptors in anxiety disorders (Felice et al. 2016). Nevertheless, to date, no indications or specific drugs based on manipulation of the $GABA_B$ receptor have been approved for use in the treatment of anxiety. Historically, it is noteworthy how the authors of a pilot study conducted in 1976, in the wake of the recent approval of baclofen in Europe and prior to the discovery of the $GABA_B$ receptor, attributed the interest in baclofen and benzodiazepines to the potential presence of common mechanisms of action. This observational double-blind, between-patient, placebo-controlled study conducted on 20 patients with schizophrenia reported an absence of differences between the two groups with regard to psychiatric conditions, observing the superiority of baclofen over placebo in the treatment of anxiety (Gulmann et al. 1976). The effects of baclofen on anxiety have recently been observed in the context of treatment for AUD (Agabio et al. 2021).

3.3.16 Substance Use Disorder

Interest in the clinical use of baclofen in substance use disorder (SUD) was fostered by a detailed body of preclinical literature and knowledge relating to activation of the $GABA_B$ receptor and inhibition of the dopaminergic brain "reward" system (see Frankowska et al. 2016). This interest, stemming from studies involving orthosteric ligands of the $GABA_B$ receptor, was further boosted by the discovery of $GABA_B$ receptor positive allosteric modulators (PAMs; see Chap. 11 of this volume). Despite the abundance of experimental literature, to date, clinical trials have only yielded partial and preliminary findings. To briefly summarize, the clinical history of the evaluation of baclofen efficacy in the treatment of SUD commenced in 1998 with a

small and open-label trial in which 10 patients with cocaine use disorder (CUD) received baclofen (20 mg, t.i.d.) in conjunction with counseling sessions for 16 weeks (Ling et al. 1998). The results of this study suggested that baclofen could be useful in reducing both cocaine craving and use (Ling et al. 1998). However, subsequent RCTs did not confirm these preliminary results; a systematic review reported that baclofen did not differ from placebo on CUD, opioid, and methamphetamine use disorders (see Agabio et al. 2013). Conversely, baclofen resulted to be effective in the treatment of nicotine use disorder and heroin withdrawal syndrome (see Agabio et al. 2013). However, since evidence on each SUD comes from a single RCT, additional surveys are needed to draw definitive conclusions.

A robust reduction in craving score was obtained in patients affected by polysubstance use disorder (PsUD) who were treated with a combination of baclofen and opipramol (Bareli et al. 2021). Lastly, several smaller clinical trials were conducted in patients with binge eating disorder and obesity. In a small open-label trial, baclofen was found to reduce the frequency of binge eating (see Agabio et al. 2013). In agreement with these findings, the findings of a study performed on obese patients revealed a significant reduction in body weight, waist circumference, appetite, and sugar cravings during treatment with baclofen (Arima and Oiso 2010).

3.3.17 Alcohol Use Disorder

A separate paragraph should be devoted to the clinical use of baclofen in AUD, in which the first studies were set up in the same time frame as clinical trials relating to the use of baclofen in SUD. Chapter 6 of this volume provides a detailed description of the therapeutic aspects and efficacy of baclofen in the treatment of AUD (see also Agabio et al. 2018, 2023).

Herein, we describe a series of aspects relating to the development of a specific baclofen-based drug, Baclocur®, currently available in France for the treatment of AUD. Baclocur®, available in 10, 20, 30, and 40 mg tablets, is a drug approved for use in France by the regulatory agency ANSM (*Agence Nationale de Sécurité du Médicament et des produits de santé*, National Agency for the Safety of Medicines and Health Products). Events leading up to the granting of marketing authorization are of particular interest in view of the singular means of dissemination of this drug. The marketing authorization process routinely adheres to a top-down approach in which an entity, usually a pharmaceutical industry, develops a drug for which marketing authorization is granted and then disseminates the product to healthcare operators, who, in turn, pass it on to their patients. However, in France, the dissemination of baclofen for use in the treatment of AUD followed a bottom-up trend and was subjected to strong patient pressure from the early stages. Starting in 2001, ANSM detected an increased off-label use of baclofen in the treatment of AUD, with this increase gradually escalating from 2008 onward. In 2011, ANSM estimated that AUD treatment accounted for 96% of off-label uses of baclofen (Villier et al. 2012; Agence Nationale de Sécurité du Médicament et des produits de santé

2017a, b). Indeed, in a retrospective analysis dated 2017, ANSM associated the increase in use of baclofen with the publication of the book entitled *Le dernier verre* (The End of My Addiction in English) by Olivier Ameisen (1953–2013), a French-American cardiologist affected by AUD.[3] In his widely circulated book, as well as in a series of articles published in scientific journals, Ameisen described how he took high doses of baclofen up to a maximum of 270 mg daily, which he subsequently reduced to 120 mg daily, ultimately resulting in him being "free of alcohol dependence symptoms effortlessly for the ninth consecutive month" (Ameisen 2005, 2008). Indeed, following the publication of Ameisen's book, data provided by both ANSM and health insurance companies responsible for reimbursing patients for medical expenses highlighted how the overall number of patients using baclofen in France had risen from approx. 45,000 in 2007 to approx. 120,000 in 2014. This increase was attributed to use of the drug in AUD, as confirmed by additional statistical analyses performed by ANSM and included in the same report (Villier et al. 2012; Agence Nationale de Sécurité du Médicament et des produits de santé 2017a). The health authorities endeavored to regulate this spontaneous phenomenon, in particular by placing emphasis on the fact that the recommended dose of 75 mg of baclofen per day should only be increased to 120 mg per day if deemed necessary in hospitalized patients (Agence Française de Sécurité Sanitaire des produits Santé 2021).

Following the authorization by ANSM of two new clinical trials, in April 2012, a multicenter, pragmatic, double-blind, randomized placebo-controlled trial (RCT) known as Bacloville was set up, providing for the recruitment of 320 outpatients from 62 French primary care centers. Patients were treated for a period of 52 weeks with doses of up to 300 mg of baclofen per day or placebo. The trial was sponsored by Assistance Publique—Hôpitaux de Paris, thus underlining the strong interest displayed by the French health authorities in regulating the use of baclofen in AUD (ClinicalTrial.gov 2014, 2017). In October 2012, ANSM authorized the setup of a second clinical trial, ALPADIR, across 32 French hospital centers. The study was designed as a multicentric RCT aimed at establishing, versus placebo, the efficacy of baclofen treatment at doses of 180 mg daily over a 20-week treatment period. A total of 316 patients were recruited to this second trial, which was sponsored by a French pharmaceutical company, Ethypharm (Reynaud et al. 2017; Rigal et al. 2020). In March 2013, ANSM announced they were preparing to grant an application for what, within the French legal framework, is known as a "*recommandations temporaires d'utilisation*" (RTU), i.e., temporary recommendations for use. This is a regulatory framework, which also exists in other countries, allowing authorities in

[3] Ameisen first heard about the use of baclofen in SUD in 2001, when a friend gave him an article published in the year 2000 in the New York Times to read. The article described baclofen as a drug candidate suitable for testing in CUD and a detail that left an impression on Ameisen, in the closing paragraph, the article cited the testimony of Mr. Coleman, a patient who used baclofen to treat spasms in his legs. Mr. Coleman had discovered that when taken a short time after cocaine, baclofen blocked the effects of and reduced craving not only for cocaine but also for for alcohol and cigarettes (Ameisen 2008).

the pharmaceutical field to authorize the prescription of a given drug to treat a prespecified indication, even in the absence of marketing authorization for the relevant drug or indication. This tool consists of an interim ruling made in the presence of strong public interest relating to the use of a given drug for which the pharmaceutical company is expected to subsequently request marketing authorization. On March 14, 2014, ANSM authorized an RTU for the use of baclofen in AUD following the publication, on March 1, 2014, of a detailed 64-page protocol establishing how patients covered by the RTU should be cared for, with the aim of providing a series of guidelines for prescribing physicians and a safety measure for patients. Ultimately, on June 13, 2014, Marisol Touraine, minister of *Affaires Sociales et de la Santé*, authorized the reimbursement of baclofen for patients who were prescribed the drug for treatment of their AUD, stating that "*se réjouit de cette grande avancée pour les patients, qui permet de répondre à une préoccupation majeure de santé publique. La France est ainsi le premier pays à reconnaître la réalité de l'utilisation de ce médicament, et son efficacité dans la lutte contre l'alcoolisme*" ("welcomes this major step forward for patients, which addresses a concern major in public health. France therefore became the first country to recognize the reality of use of this medication, and its effectiveness in the fight against alcoholism") (Agence Nationale de Sécurité du Médicament et des produits de santé 2014a, b; Journal officiel de la République française 2014; Ministère des Affaires sociales et de la Santé 2014). Later that year, once the RTU had come into force, the number of patients using baclofen to treat AUD in France rose even further. Indeed, the number of patients taking baclofen for all types of indications had risen from approx. 45,000 in 2008 to 90,000 in 2013, exceeding 120,000 by the end of 2014. These figures refer to patients to whom the drug was prescribed in line with some form of reimbursement, either by the national health service or health insurance funds, although they are likely somewhat underestimated, as some people undoubtedly paid for the drug upfront despite not being eligible for reimbursement. A recent publication examined data from the "Temporary Recommendation for Use register," indicating a discrepancy between the number of patients present on the register and the number of estimated patients mentioned above, and acknowledged by ANSM on renewal of the RTU on March 16, 2017 (Agence Nationale de Sécurité du Médicament et des produits de santé 2016, 2017b; de Beaurepaire and Jaury 2024). In October 2018, 4 years after the RTU had come into force, ANSM granted marketing authorization for Baclocur® in the wake of discussions held between ANSM, scientific organizations devoted to the study and care of AUD and patient associations; it is of interest to note how only a few months previously, the Cagliari Statement (Agabio et al. 2018) had contributed toward defining the conditions of use of baclofen in AUD. The authorization granted for Baclocur® provided for the administration of baclofen at doses not exceeding 80 mg per day. However, in June 2020, following the marketing of Baclocur®, a problem arose due to an upward tick in the bottom-up thrust, with several patient associations lodging an appeal with the *tribunal administratif de* Cergy Pontoise, demanding the withdrawal of marketing authorization due to the maximum prescribable dose of 80 mg per day representing a notable constraint for prescribing physicians. The appeal was based on the

premise that within the framework of the French experience with baclofen in AUD, the drug had habitually been administered at much higher doses, ultimately therefore placing patients at risk if physicians were bound to comply with an 80 mg per day limit. Indeed, as the series of events evolved into a legally binding process, the spontaneous patient movement that had accompanied the use of baclofen in AUD throughout France, once again came to the helm to influence proceedings. Indeed, the judges in Cergy Pontoise granted their appeal and marketing authorization for Baclocur® was withdrawn. Subsequently, the RTU framework was once again set up, with the ANSM providing recommendations to not exceed the maximum dose of 300 mg daily. This first sentence was followed by further undertakings in the administrative courts, by now the designated location in which to discuss the maximum dosage to be adopted for baclofen in the treatment of AUD. The High Court, le *Conseil d'état* subsequently passed sentence, followed by a further sentence from the *tribunal administratif de* Cergy Pontoise, finally putting an end to this process on March 4 2021, establishing that Baclocur® could be prescribed and distributed throughout all French pharmacies. A few days earlier, on February 8, 2021, the RTU had been revoked, and, lastly, on November 18, 2021, ANSM published a new set of recommendations, listed on the summary of product characteristics for Baclocur®, specifying that a daily dose of 80 mg should not be routinely exceeded, although should this not be sufficient, the patient should be referred to a multi-disciplinary team specialized in the treatment of AUD, who would be permitted to increase the dose up to a maximum of 300 mg per day (Agence Nationale de Sécurité du Médicament et des produits de santé 2021; Ministère et des Solidarités et de la Santé 2023).

3.4 The Solitude of Baclofen

Throughout the 50-year period leading up to the marketing of baclofen, no other comparable drugs have emerged for use in the treatment of consolidated or novel indications. A comparison of the pharmacology of $GABA_B$ versus $GABA_A$ receptors highlights the huge difference between the number of drugs that have been developed for the two receptors and used in the clinic, even assuming that a similar comparison may hold some significance. The pharmacology of the $GABA_A$ receptor substantially predates that of the $GABA_B$ receptor; barbital treatment was first introduced in 1902, phenobarbital, still in use today, in 1912, and chlordiazepoxide, the first benzodiazepine, was identified in the mid-1950s and introduced into clinical use in 1961, with a current estimation pointing to the synthesis of approximately 3000 benzodiazepines, 35 of which currently registered for clinical use both in Europe and the USA (Randall et al. 1960; Food and Drug Administration 2020; European Monitoring Centre for Drugs and Drug Addiction 2024). Baclofen was indeed introduced into clinical practice only a few years after the advent of benzodiazepines. A direct comparison of the therapeutic applications relating to $GABA_A$ versus $GABA_B$ receptor pharmacology is of course impossible, but it is likewise equally hard to comprehend how, over a period of 60 years, no other $GABA_B$

receptor agonists have been identified and approved for clinical use, how no therapeutic advances linked to new chemical compounds have been made. As reported by Wolfgang Froestl, "a founding father of the $GABA_B$ receptor research," from 1980 and spanning a period of approximately 20 years, researchers at Ciba Geigy/Novartis in Basel and Manchester developed a remarkable program for the synthesis and characterization of a library of $GABA_B$ receptor ligands, mainly phosphinic acid derivatives, which Froestl classified as: $GABA_B$ receptor agonists, $GABA_B$ receptor partial agonists, first generation $GABA_B$ receptor antagonists, second generation $GABA_B$ receptor antagonists, third generation $GABA_B$ receptor antagonists, as well as the first $GABA_B$ PAMs (Froestl 2010). Finally, in 1997, the Novartis scientists succeeded in cloning the $GABA_B$ receptor for the first time (Kaupmann et al. 1997). Following this extraordinary feat, baclofen has continued to stand as the sole $GABA_B$ receptor agonist approved for clinical use. Undoubtedly, significant progress has been made on a cultural and scientific level, although, to date, no further advances linked to the therapeutic use of $GABA_B$ receptor agonists have been made.

Compounds including CGP27492, CGP44532, and CGP35024 (also known as SKF97541) (Fig. 3.1) have been widely studied and employed to better characterize the action of $GABA_B$ receptor agonists both in vitro and in animal models. It might be helpful if Novartis and other pharmaceutical companies involved in the undertaking of research and development programs to investigate $GABA_B$ receptor pharmacology, were to disclose the motives that have prevented novel $GABA_B$ receptor agonists from undergoing or completing clinical development. We are currently therefore only in a position to confirm that no $GABA_B$ receptor antagonists have yet been developed for the purpose of clinical use, despite the interesting findings yielded in preliminary clinical trials (Froestl et al. 2004; see Iqbal and Gillani 2016). At the present time, therefore, a major focus is represented by the potential therapeutic application of $GABA_B$ PAMs (see Chaps. 8, 9, 10, 11, and 12 of this volume).

3.5 Prodrug and Analogs of Baclofen

It is noteworthy to underline, as mentioned previously, how both baclofen prodrugs and other drugs are assumed to act, at least partially, by interacting with the $GABA_B$ receptor.

3.5.1 Baclofen Methyl Ester

The first baclofen prodrug to be discovered was baclofen methyl ester. Studies conducted following intraperitoneal administration of this drug in the rat brain to measure brain concentrations of baclofen and its methyl ester demonstrated higher levels of methyl ester in the brain, although higher baclofen concentrations were detected in the cerebellum, thus indicating partial methyl ester hydrolysis (Leisen et al. 2003).

3.5.2 Arbaclofen Placarbil

More extensive studies have been conducted using the other baclofen prodrug, arbaclofen placarbil, a carbamate derivative of R(−)baclofen linking two specific traits to foster a more effective intestinal absorption of this active isomer of baclofen (see Corelli and Mugnaini 2016), as cited previously, a technique initially developed by Xenoport in FXS and ASD. However, although promising results were obtained in preliminary clinical trials, the development of the drug seems to have come to a halt. As of April 2024, a total of 11 clinical trials were registered both in Europe and the United States between the years 2016 and 2021, all of which aimed at treating conditions for which baclofen approval has been granted (ClinicalTrials.gov 2021; EU Clinical Trials Register 2024).

3.5.3 Lesogaberan

Another $GABA_B$ receptor agonist subjected to extensive investigation in clinical trials is lesogaberan (AZD3355), a fluorinated derivative of CGP27492 (Fig. 3.1). As mentioned above (Sect. 3.3.11), lesogaberan was first characterized in 2008 by scientists working for AstraZeneca, a company that had previously undertaken extensive research on the use of baclofen in GERD. It is noteworthy that lesogaberan was defined as a "predominately peripherally restricted $GABA_B$ receptor agonist," and consequently did not elicit the typical CNS side effects of baclofen, thus indicating lesogaberan as a potential candidate for use in the treatment of GERD. However, the effect produced by the drug was deemed insufficient, and clinical development was suspended in 2013 (see Corelli and Mugnaini 2016; Lehmann et al. 2016). More recently, the drug has been proposed for use in the treatment of non-alcoholic steatohepatitis and refractory chronic cough (Badri et al. 2021, 2022; Bhattacharya et al. 2021; see also Chap. 5 of this volume). Indeed, studies conducted with levogaberan underline an urgent need to gain further insights into the distribution and function of peripheral $GABA_B$ receptors and to investigate the therapeutic potential of pharmacological manipulation.

3.5.4 GHB

γ-Hydroxybutyric acid (GHB) is a structurally related, secondary metabolite of GABA (Fig. 3.1) known to exert effects, as shown over the last 20 years, mediated in part by $GABA_B$ receptors, although specific receptors acting as high affinity GHB binding sites have been identified in the mammalian brain (see Chap. 13 of this volume). The history of GHB marginally predates that of baclofen, being first introduced for clinical use as an anesthetic in 1964, although this use was subsequently

rejected. The drug is currently registered under the brand name Xyrem® in the EU and United States for the treatment of narcolepsy, while also being registered for use in the treatment of AUD in several countries. GHB is subject to widespread recreational use and is a potential drug of abuse. Despite the complex relationship between the effects produced by GHB and $GABA_B$ receptors, GHB does not represent an alternative $GABA_B$ receptor agonist to baclofen for use in a therapeutic setting (see Agabio et al. 2010; Baladi and Carter 2016; see also Chap. 13 of this volume).

3.5.5 Phenibut

The des-chloro analog of baclofen known as phenibut (Fig. 3.1) (see Corelli and Mugnaini 2016), a close analog of baclofen, was first synthesized as a GABA analog in Russia by Perekalin and co-workers (see Lapin 2001), although featuring a superior ability to cross the BBB than the latter. The drug was introduced into clinical use in Russia during the 1960s, where it was administered at doses ranging from 0.25 to 2 g per day as a nootropic tranquilizer-anxiolytic based on its claimed cognition-enhancing effects; it has also been used in the treatment of PTSD, depressive syndromes, and, in children, to treat hyperactivity disorders (see Lapin 2001; Kupats et al. 2020). Scarce experimental data have been made available to date, and it remains unclear whether phenibut has any other CNS binding sites in addition to $GABA_B$ receptors, with which it is known to interact. In one of the very few binding studies performed using ^{3}[H]-CGP54626 on membranes obtained from rat neurons, the K_i of racemic baclofen and racemic phenibut corresponded to 6 μM and 177 μM, respectively (Dambrova et al. 2008). More recently, phenibut has started to emerge as a potential substance of abuse capable of producing dependence and rapid withdrawal on discontinuation of the drug (see Feldman et al. 2023). Baclofen combined with a benzodiazepine is frequently administered to treat phenibut withdrawal (Kupats et al. 2020; Feldman et al. 2023). At the current state of the art, it appears unlikely that phenibut will be adopted in clinical practice as a $GABA_B$ receptor agonist alongside baclofen.

Lastly, it should be highlighted how, since their emergence in 2001, no appropriate therapeutic applications capable of paving the way to full clinical development have yet been identified for the most recent major discovery—$GABA_B$ receptor PAMs (see Chaps. 10, 11, and 12 of this volume).

3.6 Conclusions

Almost 60 years after its first synthesis, baclofen continues to represent the only compound currently in use in clinical practice in the pharmacology of the $GABA_B$ receptor. This persistent position of superiority may well be evidence of the

intuition of Heinrich Keberle and, therefore, of the fact that baclofen possesses highly singular characteristics with which no other molecule has proven capable of competing. Or indeed, might the uniqueness of baclofen be the consequence of a scarcity of extensive research programs in the field? Indeed, the most recent program was set up by Ciba Geigy in the 1980s and, while failing to identify new drugs to be used in clinical practice, led, however, to the major discovery of $GABA_B$ PAMs. Indeed, our current knowledge of the physiological functions of $GABA_B$ receptors should be closely scrutinized to pinpoint the requisites needed to attract public and private investments in research programs, as well as to further elucidate our basic knowledge of the role of central and peripheral $GABA_B$ receptors.

To reiterate a notion expressed at the beginning of this chapter, we need to verify whether the natural alkaloid for the $GABA_B$ receptor, a molecule existing in nature capable of disclosing its full potential, indeed exists and remains to be found. As an example, isoliquiritigenin (Fig. 3.1), one of a range of molecules isolated from a number of plant species present in the traditional Eastern and Western pharmacopoeia and traditionally used in Africa and Oceania, might well fit the bill, particularly as some form of activity on $GABA_B$ receptors might be justified based on the active ingredients of the compound and their traditional therapeutic use, as well as the available data indicating the apparent presence of active ingredients displaying high affinity for $GABA_B$ receptors (see Chap. 14 of this volume). It is, however, undeniable that major breakthroughs will need to be witnessed before we find ourselves once again in the position of further developing the history and pharmacology of $GABA_B$ receptors.

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