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PATENT WATCH

Selective $GABA_A$ receptor modulators: intellectual property landscape

$GABA_A$ receptor ($GABA_AR$) modulators — notably the benzodiazepines such as diazepam and alprazolam — are well-established drugs for the treatment of anxiety, epilepsy and other neurological disorders, but have side effects such as drowsiness, physical dependence and abuse potential that have been linked to a lack of selectivity for desired receptor subtypes. Given this, there have been substantial efforts in the past two decades to develop more selective $GABA_AR$-targeted therapies, with some now poised to reach the market. For example, brexanolone, developed by Sage Therapeutics for post-partum depression, has a Prescription Drug User Fee Act (PDUFA) date of 19 December 2018.

To better understand the intellectual property (IP) surrounding the use of $GABA_AR$ modulators, we generated a detailed IP landscape by reviewing and indexing English-language US, European and international (covered by the Patent Cooperation Treaty) patents and applications published in the 20-year period ending in June 2018. Our analysis was limited to filings that contain claims regarding $GABA_AR$ modulators for therapeutic use without limiting for indication. We identified 244 patent families relevant to the search focus, and then indexed these by indication and subtype of allosteric $GABA_AR$ modulator (FIG. 1a). The patent-filing activity grew dramatically through the 1990s in alignment with improved understanding of anatomical and pharmacological differences between $GABA_AR$ subtypes and their allosteric binding sites (*Neuropharmacology* **136**, 10–22; 2018). The number of patent applications per year tripled from 1998 to 2002, peaking in 2009.

A patent landscape of assignees claiming $GABA_AR$ allosteric modulators was generated from the collected set of documents. Roughly 75% of the patent applications were filed by industry (186 of 244). From a total of 81 assignees, 60% are assigned to a company (47 of 81) and nearly half of those (45%; 21 of 47) are publicly traded companies. The remaining 40% (33 of 81) of the assignees are research institutions and a few independent inventors. The space is highly fragmented: Roche is the only large (top 30 by revenue) biopharmaceutical company in the space despite the ubiquity and sales record of the older generation of drugs. Smaller companies such as Saniona A/S, Agenebio and Darth Neurosciences have a growing IP portfolio of $GABA_AR$ modulators. Ferrer International and Umecrine have the highest number of granted patents. The space is predominantly occupied by small companies focused on developing or repurposing allosteric $GABA_AR$ modulators such as SAGE Therapeutics, Marinus Pharmaceuticals, Balance Therapeutics, Anvyl and others. We anticipate that the space will remain fragmented for the foreseeable future.

An increasing percentage of documents contain claims to protect subtype-selective $GABA_AR$ modulators across a spectrum of indications (FIG. 1b). We anticipate new patent applications in the near future as a result of the elucidation of the crystal structure of a predominant isoform of $GABA_AR$ in adult human brain (*Nature* **559**, 67–72; 2018). This structure could provide valuable insights for the development of a clinical treatment for benzodiazepine overdose and further refinement of highly selective $GABA_AR$ modulators for other indications. The IP filings indicate an increasing breadth of indications, such as brain injury, eating disorders and gut motility, that may be amenable to treatment with highly selective $GABA_AR$ allosteric modulators (FIG. 1). In the meantime, a new generation of highly selective $GABA_AR$ modulators are currently being tested in clinical trials, including fast-acting antidepressants (developed by SAGE Therapeutics), anticonvulsants for an ultra-rare form of paediatric epilepsy (developed by Marinus Pharmaceuticals) and treatments for autism and cognitive disorders (developed by Roche). Positive results would re-invigorate the market for drugs modulating this long-standing clinical target.

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Competing interests
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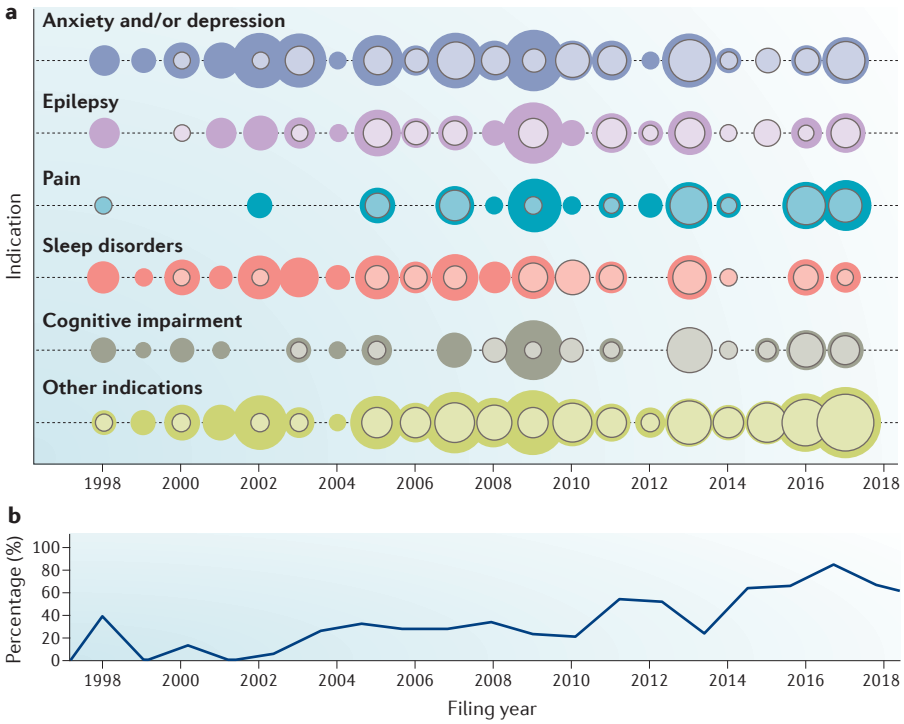

Figure 1 | **Patent filing activity for selective $GABA_AR$ modulators by indication focus and modulator type. a** | Patent documents are plotted by filing year and indication focus. The area of the bubble represents the total number of patents or applications filed. The area in the concentric bubbles indicates the number of patents or applications that claim selective modulation of $GABA_A$ receptor ($GABA_AR$) subunits. **b** | Percentage of documents with claims for selective modulation of $GABA_AR$ subunits without limiting by indication.