

## **Flupirtine as a Potential Treatment for Fibromyalgia**

LAWSON, Kim <<http://orcid.org/0000-0002-5458-1897>>, SINGH, Attam, KANTSEDIKAS, Ilya, JENNER, Christopher Arthur and AUSTEN, Daniel Keith

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## Review Article

# Flupirtine as a Potential Treatment for Fibromyalgia

Kim Lawson<sup>1\*</sup> , Attam Singh<sup>2</sup>, Ilya Kantsedikas<sup>3</sup>, Christopher Arthur Jenner<sup>2</sup> and Daniel Keith Austen<sup>2</sup>

<sup>1</sup>Department of Biosciences and Chemistry, Sheffield Hallam University, Sheffield S1 1WB, UK; <sup>2</sup>London Pain Clinic, Harley Street, London, W1G 7LD, UK; <sup>3</sup>West Hertfordshire Hospitals NHS Trust, UK

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## Abstract

Fibromyalgia is a complex disorder characterised by chronic pain, fatigue, sleep disturbance and cognitive dysfunction with limited benefit gained with current therapies. The mean global prevalence of 2.7% is estimated for this chronic condition. Pharmacological and non-pharmacological therapeutic approaches are often required as treatments of the challenges associated with fibromyalgia. Flupirtine, a non-opioid drug, exhibits effective analgesia in a range of acute and persistent pain conditions, and evidence as treatment of fibromyalgia is considered. Activation of Kv7 potassium channels and agonism at gamma-aminobutyric acid receptor A leading to indirect N-methyl-D-aspartate receptor antagonism is responsible for the analgesic effects of flupirtine and appears to be involved in other symptoms associated with fibromyalgia. Patients with fibromyalgia reported improved control of their symptoms without significant adverse effects in an observational audit in clinical practice. This article presents evidence that flupirtine, or related drugs, is a therapeutic option for the treatment of fibromyalgia. The pharmacology of flupirtine and mechanisms of action involved provide a spectrum of effects that would not only control the chronic pain characteristic of fibromyalgia but many of the other symptoms. Thus, further investigation of the efficacy of flupirtine or related drugs exhibiting a similar pharmacology as a treatment of fibromyalgia would be of interest.

## Introduction

Chronic pain affects approximately 20% of the adult population in Europe, with up to two-thirds of patients reporting dissatisfaction with current therapies.<sup>1</sup> Patients often receive complex treatment plans that combine pharmacological and non-pharmacological approaches. The limited understanding of basic underlying mechanisms and their complex interplay involved in the pathophysiology has led to chronic pain remaining a significant unmet medical need. Current therapeutic approaches for chronic pain often do not provide adequate relief and, because the central nervous system (CNS) is the location of many drug targets, various central side effects

are often experienced by patients.<sup>2</sup> As new ideas for analgesic drug design are urgently needed, the biological processes responsible for chronic pain have been the focus of preclinical research to identify potential targets for drug discovery.

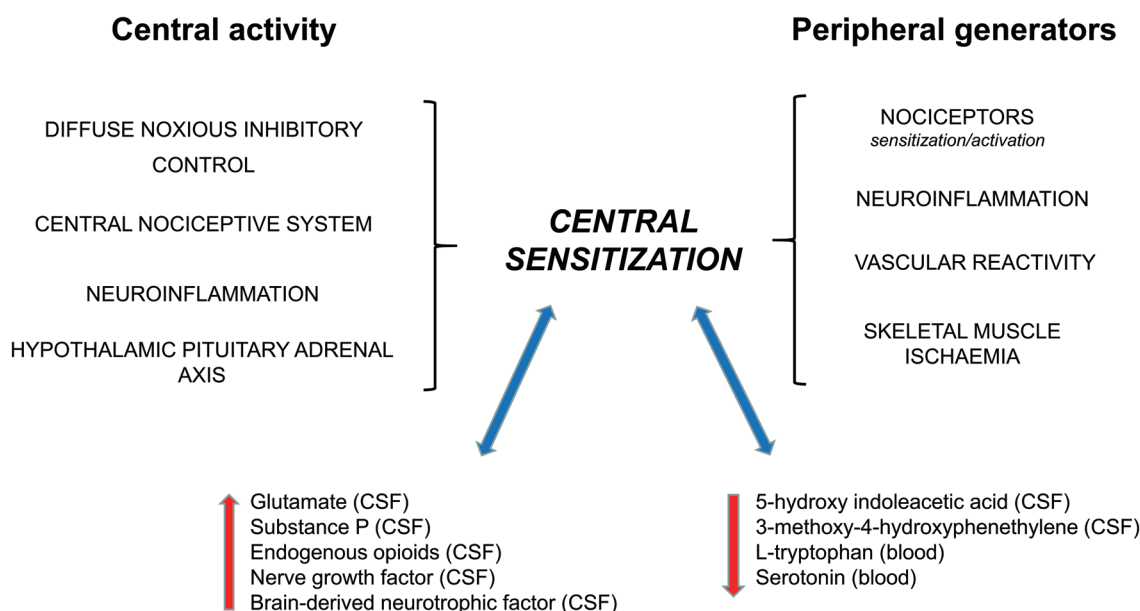
Flupirtine, a selective neuronal potassium channel opener and non-opioid analgesic, has exhibited pain relieving activity in various animal models and humans without anti-inflammatory or antipyretic properties.<sup>3-5</sup> Flupirtine was synthesized and first approved in Germany in the 1980s and is a triaminopyridine derivative with the chemical structure of 2-amino-3-ethoxy-carbonylamino-6-4-fluoro-benzylamino-pyridine. Flupirtine exhibits indirect N-methyl-D-aspartate (NMDA) receptor antagonism via activation of potassium channels, leading to the suppression of neuronal overexcitability.<sup>3,4</sup> Thus, flupirtine has been used as an analgesic for the last 35 years in the management of pain and also exerts skeletal muscle relaxation and neuroprotection properties.<sup>3-5</sup> Flupirtine is available as the maleate salt, a hydrophilic compound that is rapidly absorbed from the gastrointestinal tract with a bioavailability of 90%.<sup>6,7</sup> The volume of distribution (Vd) of 100 mg of flupirtine is 154 L in healthy volunteers and is up to 84% bound to human albumin.<sup>6,7</sup> The half-life of flupirtine depends on the route of administration, but is typically between 6.5–10.7 h. Following oral administration of 100 mg of flupirtine, clearance is 275 ml/min in healthy volunteers.<sup>6,7</sup> Flupirtine is metabolized in the liver by per-

**Keywords:** Widespread chronic pain; Fatigue; Fibromyalgia; Flupirtine maleate; Potassium channels.

**Abbreviations:** ACR, American College of Rheumatology; CNS, central nervous system; GABA, gamma-aminobutyric acid; Kv, voltage-gated potassium channels; LFT, liver function test; NMDA, N-methyl-D-aspartate.

\*Correspondence to: Kim Lawson, Department of Biosciences and Chemistry, Biomolecular Sciences Research Centre, Sheffield Hallam University, Sheffield S1 1WB, UK. ORCID: <http://orcid.org/0000-0002-5458-1897>. Tel: +44-(0)114-225-3057, Fax: +44-(0)114-225-3066, E-mail: [k.lawson@shu.ac.uk](mailto:k.lawson@shu.ac.uk)

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**Fig. 1. Pathophysiology of fibromyalgia.** Amplified neuronal excitability within the central nervous system associated with activation of peripheral generators leads to central sensitization. Altered biochemistry and neurotransmitter levels are linked to the symptoms of fibromyalgia. Raised biochemical levels are indicated by an upward facing arrow and lowered biochemical are indicated by a downward facing arrow. CSF, cerebrospinal fluid.

oxidase enzymes to the active N-acetylated analogue D13223 and 4-fluorohippuric, which are further oxidised and then conjugated to inactive metabolites. The most common adverse effects, which occurred within 6 months of treatment and are dose dependent, are dizziness, drowsiness, pruritis, dry mouth, gastric discomfort, nausea and muscle tremor.<sup>3-5</sup>

This article will consider the potential of flupirtine as a treatment for the chronic pain condition fibromyalgia. Relevant studies and publications have been identified using the search terms flupirtine and chronic pain in the literature databases MEDLINE, Web of Science, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register) and Google Scholar. In addition, evidence from a clinical observational audit is considered.

## Fibromyalgia

Chronic widespread pain is a primary characteristic of fibromyalgia, with the accompaniment of fatigue, disturbed sleep and cognitive issues.<sup>8,9</sup> The four main types of pain are nociceptive, inflammatory, neuropathic and functional. Nociceptive pain is associated with tissue damage, whilst inflammatory pain is associated with an inflammatory response. Neuropathic pain is caused by nerve irritation or damage and functional pain is pain without an obvious cause. The pain experienced with fibromyalgia is characterized by reduced pressure pain thresholds with hyperalgesia and allodynia. Fibromyalgia has been classified by the American College of Rheumatology (ACR) 1990 criteria of widespread pain (for at least 3 months) in all four quadrants of the body and pain in 11 of 18 tender point sites.<sup>10</sup> Revisions were introduced in 2010 to avoid reliance on use of tender points in assessment and to reflect the range of symptoms by including the assessment of somatic symptom severity (sleep disturbance, cognitive disturbance and fatigue) and widespread pain.<sup>11</sup> The use of a fibromyalgia symptom scale

to avoid potential misclassification of patients was the basis of further revision in the 2016 criteria.<sup>12</sup> The prevalence of fibromyalgia is 0.4–8% of the worldwide population, with a greater incidence of diagnosis in females than males.<sup>9,13</sup> The presence of co-morbidities exhibiting similar symptoms, *e.g.* chronic fatigue syndrome, often complicates the diagnosis of fibromyalgia.

Neuronal excitability due to amplified responses of the CNS to peripheral input has led to central sensitization (CS) being proposed to be involved in the pathophysiology of fibromyalgia (Fig. 1).<sup>9</sup> Peripheral sensory generators, including nerve pathologies, neuro-inflammation, skeletal muscle abnormalities and ischaemia, evoke heightened activity of the CNS leading to the symptoms of fibromyalgia.<sup>14,15</sup> Altered neurotransmitter functioning and possible neuroplasticity has been suggested to lead to the augmented sensory processing by the CNS.<sup>14</sup> Further, systemic stress-related effects, such as alterations in the hypothalamic pituitary adrenal axis, the autonomic nervous system and cardiovascular system, are also proposed to contribute to the symptoms of fibromyalgia.<sup>9,14</sup>

As with many chronic pain conditions, pharmacological and non-pharmacological therapeutic approaches are often used in the treatment of fibromyalgia.<sup>8</sup> The focus of drug therapies is often towards the treatment of pain by lowering levels of pro-nociceptive excitatory neurotransmission or/and increasing anti-nociceptive neuro-transmission rather than treating the overall condition.<sup>8</sup> An altered biochemistry in fibromyalgia is consistent with the decreased activity of the descending serotonergic-noradrenergic efferent pathways responsible for an aberrant diffuse noxious inhibitory control (DNIC).<sup>9,14</sup> Thus, current therapeutic options for fibromyalgia may modulate serotonin and noradrenaline levels, or act on voltage-gated calcium channel subunits.<sup>9</sup> Although a few drugs have exhibited efficacy in the management of fibromyalgia symptoms, the outcomes are limited with only a proportion of patients experiencing a partial reduction of symptom severity, often only marginally better than placebo.<sup>16,17</sup> The incidence of adverse effects leading many patients to discontinue use further limits the effectiveness of current medications.<sup>16,17</sup> Thus, no definitive treat-

ment or treatment algorithm exists with management guidelines indicating individualised approaches.<sup>12</sup>

Elevated glutamate, glutamine and glycine levels in pain-related brain regions, such as the posterior insula and cerebrospinal fluid, which correlate to the levels in pain in fibromyalgia, have been reported in brain spectroscopy studies.<sup>18,19</sup> Thus, in this patient group, NMDA receptors in the spinal cord and brain are exposed to raised levels of glutamate. Several drugs that downregulate NMDA receptors, such as ketamine, dextromethorphan and memantine, reduce fibromyalgia-related symptoms.<sup>20</sup> Drugs used in the management of fibromyalgia, such as gabapentin, pregabalin and certain antidepressants, reduce glutamate levels and may evoke an indirect effect on NMDA receptor activation.<sup>21,22</sup>

### Flupirtine as a treatment of pain

Effective analgesia has been reported in a range of acute and chronic pain conditions, such as musculoskeletal pain, postoperative pain, migraine and neuralgia following treatment with flupirtine.<sup>5,23,24</sup> Restoration of the normal sensitivity of over-excitabile nociceptive pathways and inhibition of the stimulation of nociceptive neurons by factors such as inflammatory mediators (*e.g.* bradykinin) have been suggested to be responsible for the effects of flupirtine.<sup>25,26</sup> In a post-marketing surveillance study of 7,806 patients, flupirtine (200–300 mg/day) exhibited effective analgesia after four weeks in more than 95% of patients with acute, subacute and chronic pain.<sup>27</sup> Clinically relevant improvements in quality-of-life and sleep were also associated in addition to a direct effect on pain with flupirtine treatment, where the incidence of adverse effects was 0.9% with no serious events reported. Thus, flupirtine is well tolerated with mild and infrequent adverse effects.<sup>28</sup> Flupirtine has been used extensively in clinical practice, as exemplified by 28.6 x 10<sup>6</sup> defined daily doses in Germany in 2010, supporting its use as a viable therapeutic treatment.<sup>29–31</sup>

Short-term flupirtine, 100 mg twice daily, treatment in patients undergoing lower limb surgery and gynaecological ambulatory surgeries reduced pain levels comparable with, and gave patient satisfaction scores similar or superior to, the non-steroidal anti-inflammatory drugs (NSAID) piroxicam and ibuprofen.<sup>24,32</sup> In both studies, there were no serious adverse effects reported with short-term (up to 5 days) flupirtine treatment. Flupirtine, at 100 mg, was reported to be preferable to pentazocine at 50 mg or tramadol at 50 mg for pain remission in controlled, double-blind clinical trials of patients with severe cancer pain.<sup>33,34</sup> In an eight day, open-label study of palliative care patients with incurable cancer, flupirtine at 100 to 300 mg, four times daily, reduced pain scores and was associated with some reduction in opioid use.<sup>35</sup> No serious adverse effects were observed and 80% of participants continued to take flupirtine after the trial with very good pain control until death. Flupirtine at 100 mg also evoked comparable efficacy to paracetamol at 1g in treating acute episodic tension-type headache or acute attacks of migraine.<sup>36,37</sup>

A meta-analysis of flupirtine in chronic pain showed that benefits were non-inferior to active comparators (*e.g.* tramadol, indomethacin, chlormezanone and pentazocine).<sup>38</sup> Studies of flupirtine in chronic pain conditions are summarized in Table 1.<sup>38–43</sup> The conditions in which flupirtine was used varied significantly but were predominantly musculoskeletal in nature, of which lower back pain, a commonly associated symptom of patients with fibromyalgia, was the most studied chronic pain condition (67.2%). In patients with lower back pain, the efficacy of flupirtine was comparative with that of tramadol and superior to placebo, whilst the

incident of treatment-emergent adverse effects and related study discontinuations was significantly lower in the flupirtine group relative to the tramadol group.<sup>39</sup> The incidence of raised liver function tests (LFTs) was comparable in the flupirtine, tramadol and placebo groups. These observations are consistent with a previous lower back pain study where comparable efficacy for flupirtine and tramadol was observed but the incidence of adverse effects related to raised LFTs and number of discontinuation post treatment were significantly higher in the tramadol group (1% with flupirtine vs 15% with tramadol;  $p < 0.001$ ).<sup>40</sup> In an open-label study of osteoporosis-related pain (low back pain, neck pain, shoulder-arm pain), efficacy of flupirtine was also observed with low reporting of adverse effects (2.4% of patients) and withdrawal from the trial (1.4% of patients).<sup>41</sup> The duration of treatment within these studies was short for chronic conditions and extrapolation of the data for a condition such as fibromyalgia may be limited. One long-term (12-month) treatment study investigated use of flupirtine in patients with chronic pain secondary to arthrosis or arthritis who had been treated with other analgesics (excluding NSAIDs).<sup>42</sup> Most of the patients showed an improvement in pain intensity following flupirtine treatment despite a high drop-out rate, primarily due to ineffectiveness or adverse effects of which dizziness was the most common and, constipation and vomiting less frequent.

Flupirtine exerts analgesic properties by activation of voltage-gated potassium channels belonging to the KCNQ Kv7 subfamily evoking hyperpolarization and stabilization of neuronal membranes, which indirectly reduces NMDA receptor activity.<sup>5,44,45</sup> NMDA receptors are a major target in the prevention and treatment of hyperalgesic pain states, thus supporting the use of flupirtine in the treatment of neuropathic pain conditions. Affinity to NMDA receptors by flupirtine has not been reported in binding studies, supporting an indirect action.<sup>46</sup> Peripheral and central nociceptive pathways contain Kv7 channels with expression in central terminals of primary afferents and dorsal horn neurons within the spinal cord.<sup>28,47–49</sup> Key locations of Kv7 channel expression in the nociceptive pathway include the thalamus, cerebral cortex and spinal cord. After peripheral injury, a decrease in expression of Kv7 channels in the peripheral nervous system, such as A $\delta$  and C fibres, contributes to increased sensory neuron excitability, which would be suppressed by activation of the remaining Kv7 channels.<sup>50,51</sup> Thus, enhancing or recovering the activity of Kv7 channels would lead to suppression of aberrant neuronal activity as observed in persistent pain conditions. Flupirtine has also demonstrated agonist properties at the gamma-aminobutyric acid receptor A (GABA<sub>A</sub>), possibly via reinforcement of GABA binding.<sup>52</sup> Studies have suggested that flupirtine prefers  $\delta$ -subunit containing GABA<sub>A</sub> receptors over  $\gamma$ -containing GABA<sub>A</sub> receptors.<sup>53</sup> The different subunit compositions define specific pharmacological characteristics such that  $\gamma$ 2-subunit containing receptors are modulated by benzodiazepines, whereas  $\delta$ -subunits are highly sensitive towards neurosteroids (brain-synthesized metabolites of ovarian and adrenal cortical steroid hormones).<sup>54</sup> These findings suggest that the pharmacological properties of flupirtine at GABA receptors differ from those of benzodiazepines. Although agonism at GABA<sub>A</sub> receptors is associated with the induction of addictive behaviours in certain drugs, such properties have had limited anecdotal reporting for flupirtine.<sup>55</sup> Analysis of the database of the German Federal Institute for Drugs and Medical Devices (BfArM) for the period 1991 to 2013 only revealed 48 reports of flupirtine abuse or dependence.<sup>56</sup> Further, treatment with flupirtine and development of addictive behaviour being *de facto* causative or mere correlation could not be clarified.

Thus, the analgesic activity of flupirtine may be due to a combined action on Kv7 channels and GABA<sub>A</sub> receptors in pain neu-

Table 1. Summary of chronic pain studies using flupirtine

Refer- ences	Type	Sample size (n) and characteristics	Method	Reported outcomes	Adverse events	Daily flupir- tine dose, mg	Comparators
Meta-analyses							
Ueberall <i>et al.</i> <sup>38</sup>	Retrospective pooled analysis	1,046 (efficacy)/1,096 (safety) patients with subacute and chronic musculoskeletal pain.	Retrospective pooled analysis of individual patient data from 8 randomized controlled (by either placebo or other analgesic) Phase III–IV clinical trials. Efficacy evaluated using primary endpoints (pain scores) as defined in the original studies. Adverse events and treatment discontinuations	For patients with subacute/chronic musculoskeletal pain, the efficacy of flupirtine was superior to placebo across its effective and approved dosage range. Flupirtine was non-inferior to the active comparators	TEAE 28.6% vs 39.1% for comparators and 17.7% for placebo. Two most commonly reported TEAEs were nausea and vertigo. TEAE-related drug discontinuations 7.1% for flupirtine vs 11.7% for comparators.	150–400	Chlormezanone 200–800 mg; Indomethacin 75 mg; Pentazocine 150 mg; Tramadol 150 mg
Trials/case reports							
Ueberall <i>et al.</i> <sup>39</sup>	Randomized, double-blind, active-/ placebo- controlled double- dummy multicentre study	363 patients with moderate-to- severe chronic low back pain (men and women 18–75-year old). Patients with organic causes of back pain and those with liver or renal impairment excluded.	Patients randomised 1:1:1 to receive flupirtine MR 400 mg, tramadol ER 200 mg, or matching placebo (each given OD in the evening) over 4 weeks. Primary endpoint was change from baseline in the LBPIX (11–point NRS) at week 4; last observation carried forward was used to impute missing scores.	Non-inferiority in LBPIX reduction compared to tramadol ER (mean ± SD: $-2.23 \pm 1.73$ vs $-1.92 \pm 1.84$ , $p < 0.001$ ) and superiority to placebo ( $-1.81 \pm$ $1.65$ , $p = 0.003$ ) on intention-to- treat analysis.	TEAE 21.0%. TEAE-related study discontinuations 3.4%. AST and ALT; elevations were noted in 51% and 58.6% of flupirtine-treated patients. Similar rates of liver enzyme elevations were noted in the placebo group.	400 (MR)	Tramadol ER 200 mg; Placebo
Li <i>et al.</i> <sup>40</sup>	Randomized, double-blind, parallel- group trial	209 subacute low back pain patients (flupirtine group = 105, comparator group = 104; mostly Han Chinese, men and women aged 18–83 years).	Patients orally treated with flupirtine vs tramadol for 5–7 days. Other analgesics and antidepressants were withdrawn. Outcome measures: patient assessment of pain intensity after 5–7 days (primary); physicians' assessment of improvement in pain and functional capacity; adverse events.	Flupirtine non- inferior to tramadol (pain relief rates of 57% (95% CI: 51–63%) and 56% (95% CI: 50–62%) respectively; $p = 0.796$ ).	Adverse event rate in flupirtine group 33% vs 49% for tramadol. Most frequently events were vertigo, nausea and vomiting (tramadol) and vertigo and nausea (flupirtine). Transient changes in white cell count (4 in tramadol group, 2 in flupirtine group) and liver enzymes (1 in tramadol group, 3 in flupirtine) were observed, which resolved after end of treatment. Discontinuation rates: flupirtine 1% vs tramadol 15%.	300 (100 TDS)	Tramadol 50 mg TDS



Table 1. Summary of chronic pain studies using flupirtine - (continued)

Refer- ences	Type	Sample size (n) and characteristics	Method	Reported outcomes	Adverse events	Daily flupir- tine dose, mg	Comparators
Ringe <i>et al.</i> <sup>41</sup>	Open-label, multicentre, prospective, observational study	869 patients with osteoporosis- related pain (81% female, mean age 67 years). No exclusion criteria.	Flupirtine up to 600 mg/ day administered for an average duration of 3 (range 2–6) weeks. VAS for pain recorded. Multivariate analyses performed to determine factors associated with VAS pain reduction.	Mean pain reduction at the end of flupirtine treatment: 43% for low back pain, 44% for neck pain, 40% for shoulder-arm pain and 40% for other pain (all reductions $p$ < 0.05 vs baseline).	2.4% reported adverse events (CNS side effects 1.3%, $n = 11$ ; GI side effects 1.1%, $n = 10$ ). 1.4% ( $n = 12$ ) withdrew from trial. No serious adverse events were reported.	270 (mean)	None
Hermann <i>et al.</i> <sup>42</sup>	Open-label, single-centre, prospective, observational study	104 patients with chronic pain secondary to arthrosis or arthritis (preliminary report from a sample of 200). Mean age 61.59 years. Excluded patients on potent analgesics (excluding NSAIDs), those with decompensated cardiovascular, liver or renal diseases, pregnant and breast- feeding women, and women not practising contraception.	12-month treatment with flupirtine followed by a 2-week period of placebo administration to assess withdrawal response. Withdrawal symptom scale completed monthly during the study then following the 2-week washout period.	55 patients completed 12-month treatment with flupirtine. 49 dropouts 75% demonstrated a response to treatment. Degree of analgesic response and doses remained constant.	The most frequent side effects were drowsiness (9% of patients), dizziness (11%), dry mouth (5%) and pruritus (9%). 49 patients dropped out: 15 due to side effects, 10 due to ineffectiveness, 7 due to side effects plus ineffectiveness, 3 due to side effects and other reasons, and 14 due to other or non-medical reasons. Lab abnormalities: transient rise in bilirubin or liver enzymes, returning to normal on study completion. Transient rise in creatinine and urea.	300	None
Stoll R. <sup>43</sup>	Open-label case series	4 fibromyalgia patients (aged 29–60, all female).	Case series in which flupirtine was added to patient's regular medications.	Reduction of pain, sleep disturbance, fatigue and depressive symptoms	Dizziness, drowsiness, pruritus, dry mouth, nausea and headache.	200 (100 BD) to 1,200 (300 QDS)	N/A

ALT, alanine aminotransferase; AST, aspartate aminotransferase test; BD, twice daily; CI, confidence interval; CNS, central nervous system; ER, extended release; GI, gastrointestinal; LBPIX, low back pain intensity index; MR, modified release; N/A, not applicable; NRS, numeric rating scale; NSAID, non-steroidal anti-inflammatory drug; OD, once daily; QDS, 4 times daily; SD, standard deviation; TDS, 3 times daily; TEAE, treatment-emergent adverse effects; VAS, visual analogue score.

ral circuits. Although flupirtine failed to exhibit affinity for  $\alpha 1$ - or  $\alpha 2$ -adrenoceptors, or serotonin 5HT<sub>1</sub> or 5HT<sub>2</sub> stimulation of inhibitory brainstem monoaminergic pathways which descend to the spinal dorsal horn associated with the diffuse noxious inhibitory control (DNIC) has been postulated as a contributory factor for the analgesic effects.<sup>28,56</sup> Further, no affinity for dopamine, benzodiazepine, opiate, central muscarinic or nicotinic receptors that have clinical relevance have been reported with flupirtine consistent with the limited adverse effect profile.<sup>28</sup>

### Flupirtine as a treatment of fibromyalgia

Evidence of effectiveness of flupirtine for the treatment of fibromyalgia is lacking with only one published open-label case study. A reduction of the symptoms of fibromyalgia following treatment with flupirtine was reported in the open-label case study,<sup>43</sup> suggesting a viable therapeutic approach (Table 1).

Having used flupirtine as an adjunct for patients with fibromyalgia in our practice, an observational audit of 14 patients offered the medication as a treatment option is presented in Table 2. Fibromyalgia was the sole condition for flupirtine use and diagnosis was made by patients meeting the ACR Diagnostic Criteria for Fibromyalgia 2010 and the absence of a possible cause noted from blood results and radiological imaging. The assessment of effectiveness was based on the patient perspective identified on co-administration of flupirtine with their current therapies. Benefit was reported throughout the period of flupirtine treatment which was the only common medication administered to all the subjects. The mean age of the patients was 53 (range: 27–72) years, of which 11 were female and three were male. Treatment duration ranged between 210 and 1,626 days up to the implementation of the European Medicine Agency's withdrawal of flupirtine-containing medications.<sup>28</sup> Dosages of flupirtine were variable (200–600 mg/day), with 100 mg at four times daily a common regimen and 50% of patients prescribed up to 600 mg within 24 hours. All patients reported 'improvement' in their symptoms following flupirtine treatment. This was self-reported, and despite the lack of numerical quantification, their persistence (up to 1,626 days) in continuing flupirtine treatment was consistent with a benefit in symptoms being gained. Thirteen patients reported an improved control of their symptoms with 50% of the cohort reporting a 'significant' to 'excellent' improvement. No significant adverse effects were reported and raised LFTs were not observed, even though 12 patients used flupirtine for 750 days or greater and eight of those patients had received treatment for more than 1,000 days continuously. Although numbers of patients in this observational audit were low, considering the higher dosages administered to and the duration of use (2–4.5 years) by the majority of the patients, the complications (rare serious liver injury) concerning the European Medicine Agency's withdrawal of flupirtine-containing products were not evident. These findings support a controlled study to evaluate flupirtine treatment in patients with fibromyalgia who are identified as flupirtine responders.

### Relevance of flupirtine to fibromyalgia

Flupirtine controlling the symptoms of fibromyalgia, particularly pain, is suggested from the included observational audit which is consistent with the observations of Stoll.<sup>43</sup> Thus, activation of Kv7 channels in nociceptive pathways by flupirtine evokes analgesic benefit to patients with fibromyalgia.<sup>57</sup> Kv7 channels have

also been identified in nodose ganglion cells where nerve fibres involved in visceral perception in the respiratory organs, gastrointestinal organs and heart originate.<sup>58</sup> Thus, the action of flupirtine on Kv7 channels, which regulate the sensitivity of visceral sensory neurons to noxious chemical and mechanical stimuli in humans,<sup>59</sup> represent an additional property for the management of pathologies which can occur as comorbidities in fibromyalgia. NMDA receptor-mediated spinal mono- and poly-synaptic reflexes were attenuated in humans by flupirtine being treated with a 400 mg oral dose, suppressing rigidity in skeletal muscle and subsequent akinesia.<sup>60,61</sup> The skeletal muscle relaxant and analgesic properties of flupirtine are demonstrated in the same dose range, and thus would be applicable in the treatment of fibromyalgia.

Reductions in gray matter volume, particularly in the anterior cingulate cortex, the prefrontal cortex and the insula areas of the brain, are consistently observed in patients with fibromyalgia.<sup>62</sup> The atrophy in pain-related brain areas in fibromyalgia has been suggested to contribute to some of the symptoms.<sup>63</sup> Flupirtine has been reported to exhibit neuro-protective activity in a variety of neurodegenerative disease models due to indirect antagonism of NMDA receptors, upregulation of the anti-apoptotic protein B-cell lymphoma 2 (Bcl2) and antioxidant activity via increased glutathione levels.<sup>64–67</sup> These effects are suggested to be due to mechanisms such as prevention of intracellular calcium overload and oxidative stress reduction associated with the analgesic properties of flupirtine.

### Potential limitations of flupirtine

Mild increases in liver enzymes, bilirubin and creatinine have been observed in some patients, but are usually not viewed significant enough to interrupt treatment.<sup>68</sup> Flupirtine has however been associated with very rare cases of severe drug-induced liver injury due to hepatotoxic metabolites.<sup>69,70</sup> The incidence of flupirtine-related hepatobiliary adverse events in the BfArM database was estimated to be about eight in 100,000 patients (>0.01%).<sup>71</sup> The reactive metabolites responsible for liver injury are detoxified via glutathione and thus, sufficient cellular glutathione stores will limit hepatotoxicity.<sup>70</sup>

The European Medicines Agency's Pharmacovigilance Risk Assessment committee recommended risk minimization measures (RMM) for flupirtine (use only after other analgesics were trialed, patients restricted to up to two week-long treatments, with weekly LFT) due to concern of rare serious liver injury associated with long-term use of flupirtine.<sup>28</sup> Limited adherence to the RMM led to withdrawal of flupirtine-containing medications from the European market in 2018.<sup>28</sup> Serious liver injury, however, was not seen as a complication in the studies discussed above.

### Future directions

The complex heterogenous disorder fibromyalgia is currently medically unmet with limited benefit gained from available therapies. The diversity of the symptoms of fibromyalgia and the related physiology suggests that to achieve effective therapeutic control drug treatments need to target multiple events, which has led to combination therapy as a standard approach. Kv7 channel activation alone or in combination with other pharmacological mechanisms of action, as exemplified by flupirtine, appears to exhibit a spectrum of pharmacology beneficial to patients with fibromyalgia that responded to this treatment. Development of novel Kv7

Table 2. Observational audit of flupirtine treatment in patients with fibromyalgia in our clinical practice

Age/sex	Flupirtine dose (mg) treatment duration	Other medications	Therapeutic effect	LFTs and adverse reactions	Diagnosis
52/F	100 QDS then MR 400 OD (767 days)	Pregabalin 200 mg OM/300 mg ON; Amitriptyline 50 mg ON; Codeine 15–30 mg QDS PRN	Baseline “pain score” 16/18 “overall having a better time, there has been some improvement”	ALT 39 03/18. Normal prior to that.	Fibromyalgia
72/F	100 up to 6 times/day; Then MR 400 + IR 100 BD PRN (1,626 days)	Butrans buprenorphine transdermal patch 20 µg/hour 1 patch every 7 days; Nortriptyline 10 mg OD	“Beneficial”, keeping well and active, and doing lots of walking and gardening. Forced to reduce dose to MR 200 mg (in 2015 difficulties funding the prescription)—return of symptoms. Improved once dose increased back to MR 400 mg.	Normal LFTs throughout.	Fibromyalgia; Low back pain; Osteoarthritis (knees)
53/F	100 mg QDS (1,292 days)	Pregabalin 100 mg BD; Tapentadol 12.5 mg lunch and afternoon; Tapentadol 50 mg ON; Diazepam 5 mg PRN; Versatis (lidocaine) 5% topical patch 12 hrs/day; Zomorph (morphine sulphate MR) 10 mg ON	Successful in reducing the pregabalin and tapentadol dosages, in particular tapentadol. She has been reducing steadily over the last 3 years.	Normal LFTs	Fibromyalgia CRPS (lower limb); Pigmented villonodular synovitis; Degenerative disc disease in the cervical and lumbar spine
48/F	100 mg up to 6 times/day (751 days)	Pregabalin 300 mg BD; Duloxetine 120 mg OD; Zopiclone 7.5 mg ON PRN; Metoclopramide 10 mg TDS PRN; Tapentadol 50 mg BD	Pain score pre-flupirtine 8/10; Pain is under better control and her mobility has improved (14/09/2016)	Normal LFTs	Fibromyalgia; Chronic migraine
36/F	100 mg TDS PRN (1,029 days)	Duloxetine 50 mg OD (and weaning); Meds before established on flupirtine: Amitriptyline 20 mg ON; Duloxetine 120 mg OD; Tapentadol 50 mg PRN (up to 400 mg)	“Excellent progress, pain & other symptoms from the fibromyalgia much improved. Recently completed a 2 hours bike ride.” Patient very disappointed to learn flupirtine was discontinued.	Normal LFTs. Stomach pain, headaches, muscle twitches and trembling initially.	Fibromyalgia
27F	100 mg up to 6 times/day (449 days)	Dihydrocodeine MR 90 mg BD; Fluoxetine 60 mg OD; Diazepam 5 mg TDS PRN; Morphine (Oramorph) 2.5–5 mL TDS PRN; Meds before established on flupirtine: Baclofen 10 mg up to 6 times/day; Duloxetine 120 mg OD; Paracetamol 1 g QDS; Propranolol 40 mg TDS; Calceos 2 tabs OD	“... found the flupirtine to be of significant benefit reducing her pain and fatigue by approximately 40–50%”	Normal LFTs	Fibromyalgia; Hypermobility syndrome
54/M	100 mg 6 times/day (to TDS at time of discontinuation) (1,598 days)	Amitriptyline 120 mg ON; Naproxen 500 mg BD PRN; Omeprazole 20 mg OD; Pregabalin 150 mg BD	Refractory fibromyalgia, eventually symptoms sufficiently controlled to allow return to work, light exercise.	Normal LFTs; Sleepy and agitated for approximately an hour after 3 <sup>rd</sup> dose	Fibromyalgia



Table 2. Observational audit of flupirtine treatment in patients with fibromyalgia in our clinical practice - (continued)

Age/sex	Flupirtine dose (mg) treatment duration	Other medications	Therapeutic effect	LFTs and adverse reactions	Diagnosis
66/F	100 mg BD (1,304 days)	Ibuprofen 200 mg PRN (1,200 mg max/24 hours)	"Finding flupirtine to be of benefit ... fibromyalgia symptoms seem to be under relatively good control ... doing extremely well."	Normal LFTs	Fibromyalgia
52/F	100 mg up to 6 times/day (1,360 days)	Gabapentin 200 mg TDS	"...small improvement, with the addition of flupirtine, of approximately 15–20%" – on initiation. "... has not had any pain for some time ..." – after 3 years of treatment. Fibromyalgia pain recurred after discontinuing flupirtine.	Normal LFTs	Fibromyalgia
64/F	100 mg QDS (750 days)	Zopiclone 3.75 mg OD PRN; Tapentadol 50 mg TDS–QDS	Some improvement overall with starting the flupirtine, tapentadol requirements have reduced.	Normal LFTs	Neuropathic pelvic pain; ME
64/F	100 mg QDS (1,565 days)	Amitriptyline 10–20 mg ON; Diazepam 5 mg PRN; Ibuprofen 400 mg TDS PRN; Epilim (valproate) 400 mg BD; Amlodipine 5 mg OD; Zopiclone 10 mg OD PRN	"Flupirtine does take the edge off her pain."; Patient's own words: "it is the only thing that gives me a little relief"; NB. Patient with complex chronic pain who experienced adverse effects with a number of medications.	Normal LFTs	Fibromyalgia; Myofascial pain syndrome; CFS; TMJ; Epilepsy (controlled); IBS; Central hypersensitivity syndrome
59/F	100 mg 4–5 times/day (896 days)	Dihydrocodeine 15–30 mg QDS PRN	"...treated with the medication flupirtine on which she was stable & doing extremely well in terms of efficacy & minimal adverse effects"	Normal LFTs	No diagnosis recorded
53/M	100 mg 4–5 times/day (1,418 days)	Tramadol 50 QDS; Trazadone 100 mg ON; Cyclobenzaprine 2.5 mg ON; Zolpidem 10 mg ON	"...pain is under good control, with over 90% pain relief."	Normal LFTs	Fibromyalgia
43/M	100 mg 6 times/day (210 days)	Low-dose naltrexone 3 mg OD	"... overall pain score has dropped from approximately 7 out of 10 to approximately 2/3 out of 10."	Normal LFTs	Fibromyalgia

Fibromyalgia was the sole condition for flupirtine use and diagnosis was made by patients meeting the diagnostic criteria set out in the American College of Rheumatology Diagnostic Criteria for Fibromyalgia 2010 and the absence of a possible cause noted from blood results and radiological imaging. The assessment of effectiveness was based on the patient perspective identified on co-administration of flupirtine with current therapies. Informed consent was obtained from individuals included in the observational audit. In the 'therapeutic effect' column, patient comments are indicated in quotation marks. ALT, alanine aminotransferase; BD, twice daily; CFS, chronic fatigue syndrome; CRPS, chronic regional pain syndrome; F, female; IBS, irritable bowel syndrome; IR, immediate release; LFT, liver function test; M, male; ME, myalgic encephalopathy; MR, modified release; OD, once daily; OM, every morning; ON, every night; PRN, as needed; QDS, 4 times daily; TDS, 3 times daily; TMJ, temporomandibular joint.

channel activators has gained interest, which could offer additional approaches for the management of complex clinical conditions.<sup>72</sup> Thus, investigation in patient responders of the efficacy of flupirtine, or related drugs exhibiting a similar pharmacology, as a treatment approach would be of interest.

## Conclusion

Flupirtine, an indirect NMDA receptor antagonist due to Kv7 channel activation and GABA<sub>A</sub> receptor agonism, is a novel analgesic medication with utility in the treatment of patients with fibromyalgia who have often proven refractory to standard anti-neuropathic pain medications.

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## Conflict of interest

The authors have no conflicts of interest related to this publication.

## Author contributions

DKA and KL proposed the aim of the work; AS, IK and KL carried out the literature search; AS, IK and CAJ evaluated and assembled the contents of Tables 1 & 2; KL wrote a draft of the manuscript that all authors contributed comments to. All authors were involved in the manuscript preparation, and have read and approved the manuscript.

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