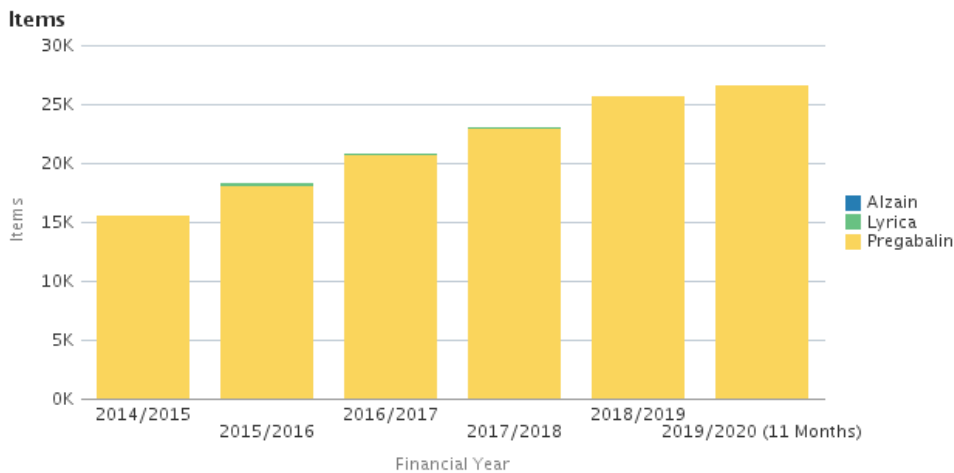


Audit: Pregabalin Prescribing on the Isle of Man

Background

Prescribing of pregabalin on the Isle of Man has increased substantially over the last few years, with a 70% increase in prescriptions over the last 6 years, increasing by over 2000 prescriptions every year. Although the price of pregabalin reduced dramatically in 2017 the cost of pregabalin in 2019/2020 was over £91,000.(from EPACT2)



The Isle of Man is spending more on pregabalin than all other areas in England and Wales.



Pain Visual Snapshot


Period From:
April 2020

Period To:
March 2021

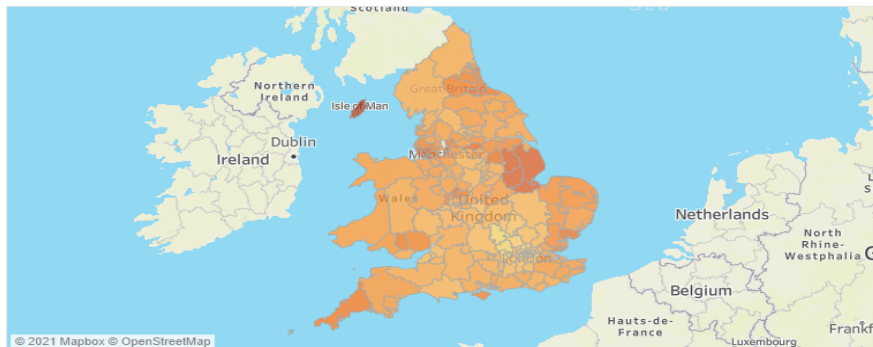
Select Commissioner Grouping:
ALL (INCLUDING OLD CCG BOUNDARIES)

Financial Comparison Denominator:
Cost per 1,000 Patients

Select Category:
Pregabalin

£157  £1,097

Commissioners mapped and filtered to show Cost per 1,000 Patients April 2020 to March 2021



| | | |
|---|---|--------|
| ANEURIN BEVAN HB | ANEURIN BEVAN HB | £596 |
| BETSI CADWALADR UNIVERSITY HB | BETSI CADWALADR UNIVERSITY HB | £476 |
| CARDIFF & VALE UNIVERSITY HB | CARDIFF & VALE UNIVERSITY HB | £419 |
| CWM TAF MORGANNWG HB | CWM TAF MORGANNWG HB | £636 |
| HWEL DDA HB | HWEL DDA HB | £475 |
| ISLE OF MAN | ISLE OF MAN | £1,097 |
| NHS BARNSELY CCG | NHS BARNSELY CCG | £725 |
| NHS BASILDON AND BRENTWOOD CCG | NHS BASILDON AND BRENTWOOD CCG | £480 |
| NHS BASSETLAW CCG | NHS BASSETLAW CCG | £678 |
| NHS BATH AND NORTH EAST SOMERSET, SWINDON AND WILTSHIRE CCG | NHS BATH AND NORTH EAST SOMERSET CCG (OLD CCG BOUNDARY) | £249 |
| | NHS BATH AND NORTH EAST SOMERSET, SWINDON AND WILTSHIRE C.. | £402 |
| | NHS SWINDON CCG (OLD CCG BOUNDARY) | £479 |
| | NHS WILTSHIRE CCG (OLD CCG BOUNDARY) | £430 |
| NHS BEDFORDSHIRE, LUTON AND MILTON KEYNES CCG | NHS BEDFORDSHIRE CCG (OLD CCG BOUNDARY) | £261 |
| | NHS BEDFORDSHIRE, LUTON AND MILTON KEYNES CCG | £275 |
| | NHS LUTON CCG (OLD CCG BOUNDARY) | £280 |
| | NHS MILTON KEYNES CCG (OLD CCG BOUNDARY) | £293 |
| NHS BERKSHIRE WEST CCG | NHS BERKSHIRE WEST CCG | £396 |
| NHS BIRMINGHAM AND SOLIHULL CCG | NHS BIRMINGHAM AND SOLIHULL CCG | £428 |

The MHRA drug safety update for pregabalin and gabapentin advises that patients should be carefully evaluated for a history of drug abuse and observed for possible signs of misuse, abuse, or dependence. Due to these risks as of April 2019 pregabalin and gabapentin became Schedule 3 controlled drugs. Reports of abuse and dependence are higher for pregabalin than gabapentin.¹ On the Isle of Man Prescribing of gabapentin has remained at consistent levels and much lower amounts than pregabalin, which is consistent with the evidence that pharmacodynamically pregabalin is more prone to abuse, but also more dangerous in overdose.^{2,3,4}

Studies have shown that risk of abuse with pregabalin is much higher in opioid users and the majority of case reports concerning abuse of pregabalin involved patients with a history of substance abuse.^{3,4} Pregabalin can cause euphoric and dissociative effects when taken in doses higher than normal therapeutic doses.^{2,3,4} Misused pregabalin has been found to be most often obtained from healthcare providers.⁴ Off-label use also increases the number of patients exposed to pregabalin.

Overdose and deaths involving pregabalin have occurred on the island, overdose deaths are more common when taken with other CNS depressants particularly opioids. This audit aims to assess the appropriateness of pregabalin prescribing on the Isle of Man.

Standards

| Criteria | Standard |
|--|----------|
| Indication for prescribing pregabalin is documented in the clinical record | 100% |
| Pregabalin is prescribed for a licensed indication | 100% |
| Prescriptions do not exceed the licensed therapeutic maximum dose of 600mg | 100% |
| Quantities being supplied don't exceed prescribed dose | 100% |
| Prescribed treatments follow guidelines – patients have tried, or been excluded from taking, 2 previous medicines prior to being prescribed pregabalin | 100% |
| Medication is reviewed at least once in the last year | 100% |

Method

Standards were created from national guidelines.^{1,2,5,6,7,8}

A search in EMIS in GPs supported by the primary care pharmacy team to identify all patients currently prescribed pregabalin. A random sample of these was taken to ensure 99% confidence level with a 5% error margin using the Raosoft sample size calculator. (<http://www.raosoft.com/samplesize.html>)

The primary care pharmacy team completed data collection spreadsheets for each of the supported GP surgeries. Further information was obtained from the mental health service RiO notes where needed.

Data was collected in June and July 2020.

Results and discussion

A total of 1209 people have pregabalin currently prescribed on their GP EMIS record. 977 of these are in primary care pharmacy supported surgeries. A total of 400 were analysed in the sample.

| Criteria | Standard | Finding |
|--|----------|---------|
| Indication for prescribing pregabalin is documented in the clinical record | 100% | 46% |
| Pregabalin is prescribed for a licensed indication | 100% | 43% |
| Prescriptions do not exceed the licensed therapeutic maximum dose of 600mg | 100% | 100% |
| Quantities being supplied don't exceed prescribed dose | 100% | 90% |
| Prescribed treatments follow guidelines – patients have tried, or been excluded from taking, 2 previous medicines prior to being prescribed pregabalin | 100% | 42% |
| Medication is reviewed at least once in the last year | 100% | 69% |

Indications for prescribing pregabalin and is this within license

46% had the indication for pregabalin being prescribed documented in the active problem list on EMIS. Others were in past problems, yet pregabalin is still being prescribed. For reviews of medication the indication should be an active problem and clearly documented. Some of the indications were worked out by the audit team by reading through notes to decide what the pregabalin was for, in 2% of patients the indication was unable to be found or worked out.

EMIS has functions such as linking indications to medication, which would make the indication clear for each medicine, but this appears to be rarely used.

43% had pregabalin prescribed for a licensed indication, meaning over half of prescribing is for off-label indications.

Figure 1 Pain or mental health related indication

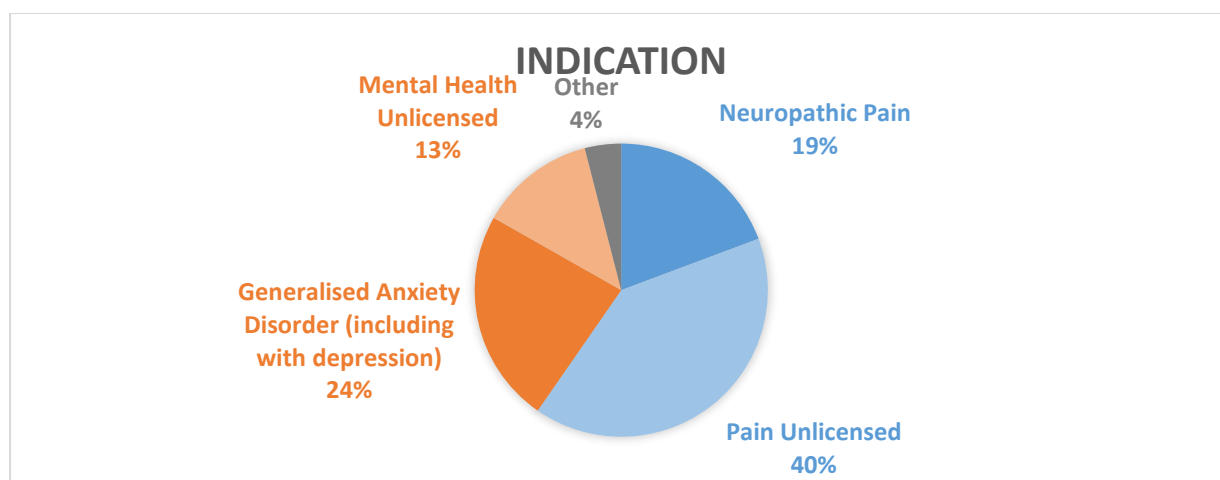


Figure 1 shows 59% of prescribing is for pain related indications and 37% is for mental health related indications.

Figure 2 Indications for prescribing pregabalin

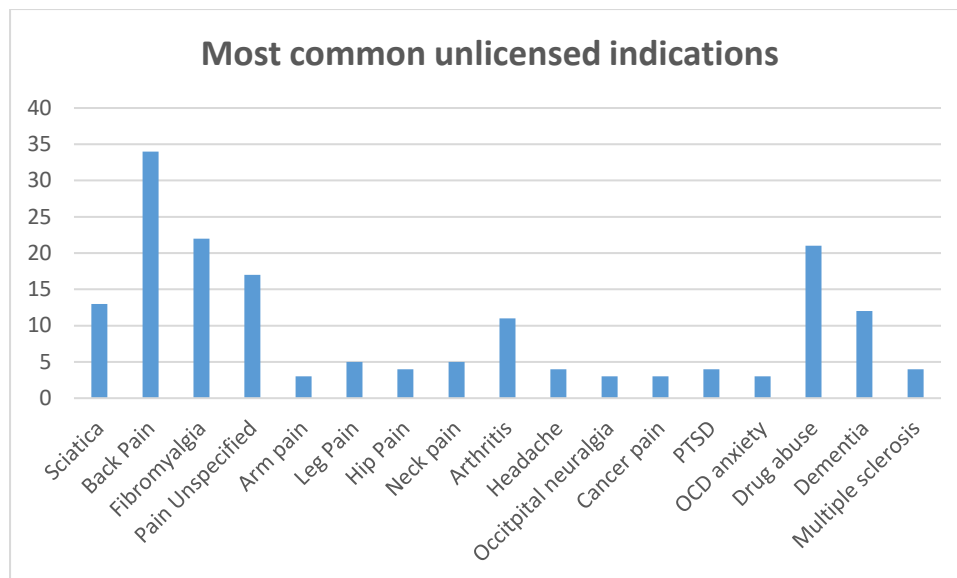
| | | | |
|------------------------------|------------------------------|-------------------------------------|--------------------------------------|
| Neuropathic Pain | Diabetic Neuropathy | Post-herpetic Neuralgia | Licensed Indication 43% |
| Carpal tunnel Syndrome | Phantom Limb Pain | Trigeminal Neuralgia | |
| Generalised Anxiety Disorder | Anxiety with Depression | Epilepsy | |
| Sciatica | Back Pain | Fibromyalgia | |
| Pain - unspecified | Chronic pain | Arm pain | Unlicensed Indication 57% |
| Leg pain | Hip pain | Facial Pain | |
| Neck Pain | Toe Pain | Foot/ankle pain | |
| Shoulder pain | Arthritis | Joint Pain | |
| Headache | Migraine | Spondylitis | |
| Spondylosis | Osteomyelitis | Occipital Neuralgia | |
| Sickle Cell associated pain | Guillain-Barré Syndrome | Knee Dislocation | |
| Leg Fracture | Motor neurone disease | Inflammatory Bowel Disease | |
| Cancer pain | Pancreatitis | Jolting | |
| Breast pain | Abdominal pain | Sudeks Atrophy | |
| Stiff neck | Reflex sympathetic dystrophy | Pelvic pain | |
| Burning feet syndrome | SAPHO | Temporomandibular joint dysfunction | |
| Regional pain syndrome | Muscle twitch and groin pain | Akathesia | |
| PTSD | Social anxiety | OCD anxiety | |
| Drug abuse | Agitation in dementia | Adjustment disorder | |
| Personality disorder | Schizophrenia | Bipolar disorder | |
| Tired all the time | Organic Delusional Disorder | Multiple Sclerosis | |
| Tremor | Unknown | | |

Figure 2 shows the wide range of indications patients are being given pregabalin for – with the majority being unlicensed with little or no evidence base.

It has been postulated that characteristics that contribute to the appeal of pregabalin being abused include the relative ease of obtaining large quantities, low cost and frequent off-label use, which increase the number of patients exposed to pregabalin.⁴

This major use of off-label indications for pregabalin on the Isle of Man should be minimised. If a decision is made to prescribe the drugs for unlicensed indications, prescribers should follow relevant professional guidance, taking full responsibility for the decision.⁸

Figure 3



There is moderate quality evidence to support the use of pregabalin in neuropathic pain, with nearly 4 out of 10 people achieving at least 50% pain relief.⁹ There is much less evidence to support use in fibromyalgia, with reports of only 1 in 10 patients experiencing at least a 30% reduction in pain.⁹ No treatment benefit has been found for back pain, sciatica, spinal stenosis or migraine⁹, yet these are some of the most commonly unlicensed indications for pregabalin prescribing on the Isle of Man, as shown in figure 3. Other interventions more likely to help such as physical rehabilitation for back pain and musculoskeletal pain should be considered.⁸

3% of pregabalin prescriptions were for use in dementia such as to manage agitation and BPSD. This isn't a licensed indication and not recommended in guidelines. A search for evidence to support this prescribing may be needed. 42% of people on pregabalin for dementia were on liquid form, which will increase the cost of using pregabalin in this area, due to the cost of the liquid.

Doses

Doses were checked to see if high doses were being prescribed which may indicate potential of abuse being used for euphoria. 100% of pregabalin prescriptions were within the maximum dose of 600mg (1 case potentially above 600mg). A positive result, and compares well to other country findings such as Sweden which showed 8.5% of prescriptions above 600mg and the UK is reported to have 1% receiving prescriptions over 600mg.⁴

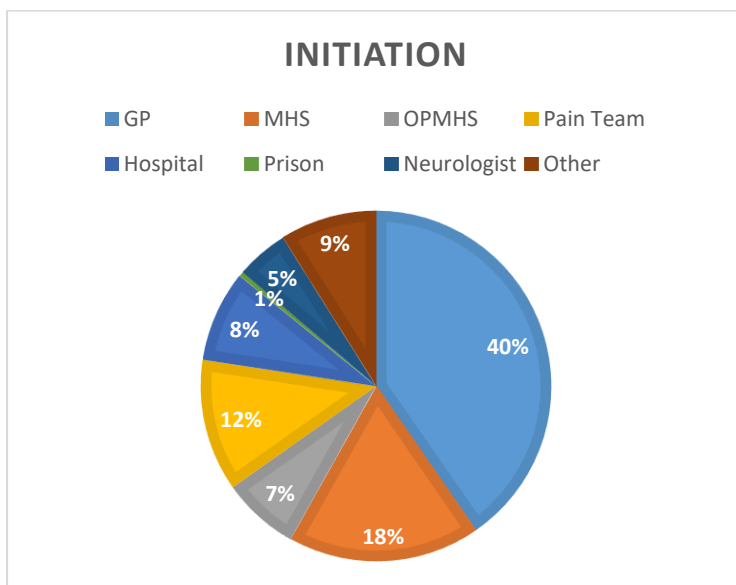
| Daily Dose | Number of patients | % |
|------------|--------------------|----|
| OD | 45 | 11 |
| BD | 234 | 59 |
| TDS | 119 | 30 |
| QDS | 2 | 1 |
| <150mg | 90 | 23 |
| 150-300mg | 175 | 44 |
| 301-600mg | 133 | 33 |
| >600mg | 1 | 0 |

The therapeutic range is thought to be 150mg-600mg. Almost a quarter of prescriptions were for less than 150mg, potentially under dosing. A Cochrane review has shown that 150mg daily was generally ineffective for pain.¹⁰ Also 11% of patients were receiving once daily prescriptions, according to the Summary of Product Characteristics the pharmacokinetics of pregabalin guide two or three times a day dosing, therefore once daily doses could be resulting in periods of sub-therapeutic treatment. Review and optimisation of these reasonably high proportions of low dose and low frequency prescriptions is needed.

30% were given three times a day doses. Although this is within the licensed dose frequency according to the SPC, twice daily dosing is adequate and shows similar efficacy and tolerability to three times a day dosing.¹¹ So there is potential to reduce the tablet burden for patients, improve the chance of compliance with BD vs TDS dosing for the patient, and reduce cost by a third for each of these patients. Less capsules supplied would also mean less capsules available for possible diversion

Where is pregabalin initiated and when

Figure 4



Majority of prescription are started by GP, which is understandable as they are most often seeing patients.

Figure 5

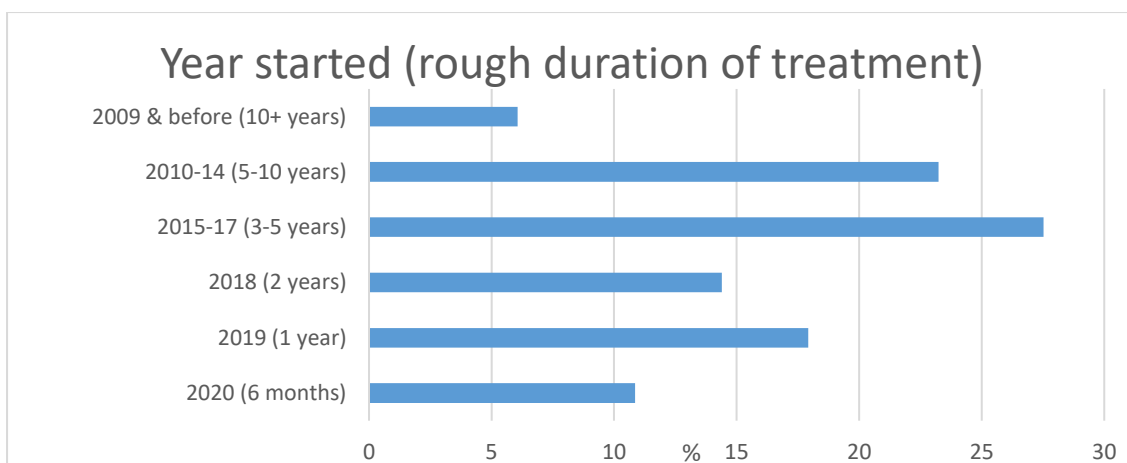


Figure 5 shows 57% of patients have been taking pregabalin for over 3 years. The majority of prescriptions are for pain related indications. Guidance for use in neuropathic pain suggest pregabalin should be stopped after 8 weeks if sufficient benefit isn't shown, and a reduction on an annual basis to ascertain ongoing effectiveness.² The initial benefit some patients obtain from treatment may not continue.

This audit found that 69% of patients had had a medication review within the last year. However it wasn't always clear if pregabalin in particular had been reviewed for effectiveness, as any mention of a review of medicine was counted and further details weren't always included. Targeting potential candidates for trial reduction could be tried – with clearer documentation of annual reviews and attempts of reduction of pregabalin.

Place in therapy

Pregabalin is not recommended first line treatment for either neuropathic pain or generalised anxiety disorder. NICE guidelines for generalised anxiety disorder recommend it as third line treatment after SSRIs and SNRIs.⁶ For neuropathic it is recommended to use a tricyclic antidepressant, such as amitriptyline, and gabapentin before pregabalin, and also duloxetine before pregabalin when for diabetic neuropathy.^{5,7,8}

Overall 42% of patients at least two other appropriate medication had been seen to be tried before, indicating it was being used third line as per guidelines:

- 48% of patients having pregabalin for the licensed indication of anxiety had tried two other appropriate medications before
- 43% of patients having pregabalin for the licensed indication of neuropathic pain had tried two other appropriate medications before

This shows that it is likely that in over half of patients being prescribed pregabalin guidelines aren't being followed.

Potential of substance misuse and co-prescribing with opioids and benzodiazepine

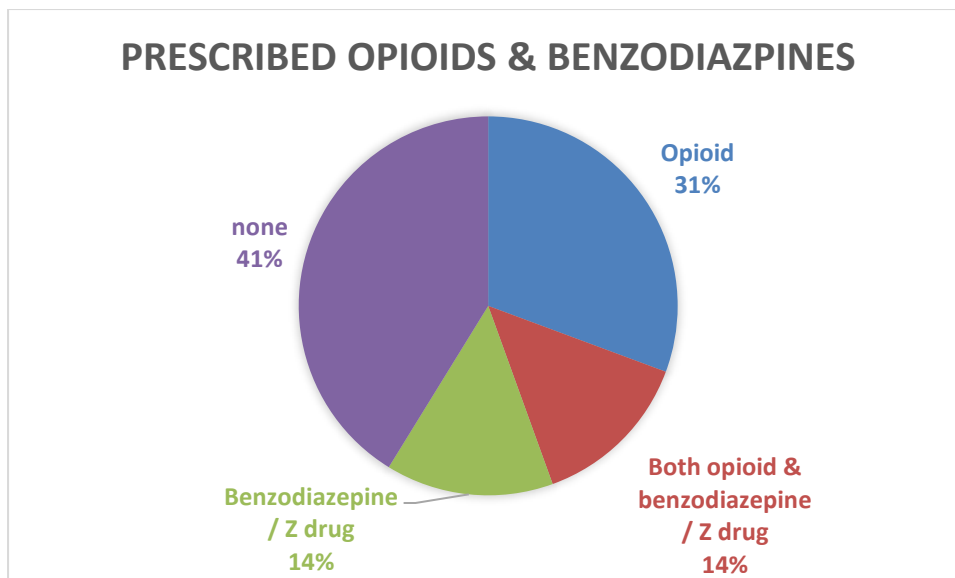
30% of the sampled patients prescribed pregabalin had potential risk of abuse signs including evidence of drug or alcohol abuse, 'missing'/'lost'/'stolen' scripts or medicine and requesting extra.

Pregabalin should be prescribed with caution in patients with a history of substance abuse and monitored for symptoms of pregabalin abuse.^{1,12}

Prescribing for patients with potential for misusing, diverting or becoming dependent may increase the risks from their use. However, such patients may also have higher prevalence for the indicated conditions so may still gain benefit from pregabalin. Patients shouldn't automatically be excluded from access to medications because of potential signs of abuse; however it should be a relevant consideration when deciding on whether to prescribe pregabalin. Less harmful, alternative drugs can often be used.²

Co-prescribing of opioids and benzodiazepines was examined. It is known that risk of abuse with pregabalin is much higher in opioid users, and benzodiazepines are well known to be diverted and abused. All are CNS depressants and combination greatly increases risk, risk of respiratory depression is increased with pregabalin in combination with these medicines.

Figure 6



As seen from figure 6 over half are prescribed an opioid or benzodiazepine with their pregabalin. The main indication is pain related so may expect co-prescribing of other painkillers –however guidelines do not recommend opioids for neuropathic pain which is the licensed indication for pregabalin.

44% were prescribed concomitant opioids, of these 31% also had a benzodiazepine or Z-drug. In an audit of gabapentinoids use in prison, where substance misuse is known to be high, and opioids are highly sought after – 49% of prisoners were also taking an opioid.¹³ This is a comparable figure to the 44% found on the Isle of Man, even though this is a primary care audit of the general public and not focusing on a higher risk group such as prison.

Conclusion and Recommendations

Clearer documentation of the indication for prescribing pregabalin, both in EMIS and RiO, would be valuable. This would also facilitate annual reviews to be carried out easier. Functions such as linking indications to medication on EMIS could be used.

Annual medication reviews need to be clearly documented to be reviewing pregabalin and evidence of annual attempts of reduction. This could be started by selecting patients taking pregabalin over 12 months for pain and trial withdrawal. Patient leaflets are available such as the Live Well with Pain leaflet: <https://livewellwithpain.co.uk/resources/resources-for-patients/six-questions-to-ask-yourself/>

Dose optimisation reviews are needed for some – those on less than minimum recommended dose, those on once daily dosing, and those on more than BD dosing – cost savings and improved patient compliance.

A reduction in the high proportion of co-prescribing pregabalin and opioids and benzodiazepine will greatly reduce risks.

Consider alternative options for those who are potentially abusing or diverting pregabalin.

Review what treatment pathways are being followed by prescribers on the Isle of Man. Guidelines don't appear to be being followed. There is a huge amount of off license prescribing with pregabalin that should be minimised, to reduce the amount of inappropriate pregabalin being available for potential abuse.

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