Prescribing Pearls for Primary Care

Medscape UK X Guidelines
Primary Care Hacks

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1. Low-dose mirtazapine has a greater sedative effect than higher-dose mirtazapine

Mirtazapine is a commonly used atypical antidepressant. Because it has sedative, antiemetic, anxiolytic, and appetite-stimulating properties, it is often used for depression complicated by anxiety, insomnia, poor appetite, and/or weight loss.[1] Mirtazapine is also used to augment other antidepressants (e.g. SSRIs or SNRIs) in major depression, although the evidence for efficacy is mixed.[2]

Low-dose mirtazapine (i.e. ≤15 mg) has high affinity for sedating histamine receptors.[3,4] However, at higher doses (i.e. ≥30 mg), mirtazapine has an increased noradrenergic effect that blunts this sedative effect, and may be overstimulating in older adults.[3,4]

Consequently, low-dose mirtazapine can improve sleep efficiency, total sleep time, and sleep quality.[3,4] This effect is most noticeable in the first few weeks of therapy.[3]

Although low-dose mirtazapine may be subtherapeutic for depression, it can help to manage associated symptoms of insomnia and anxiety.

2. CCBs and losartan have urate-lowering properties

Hypertension affects nearly three-quarters of people living with gout, and it is well established that certain antihypertensives (i.e. diuretics and beta-blockers) can increase serum urate levels and worsen gout risk.[5] Other medications that have been associated with an increase in serum urate include:[5,6]

- bempedoic acid
- ACEis
- non-losartan ARBs.

In contrast, CCBs and losartan have been associated with a lower risk of incident gout among people with hypertension.[5] Statins (particularly atorvastatin), fenofibrate, and SGLT2is have also demonstrated urate-lowering properties.[7–9]

Losartan and CCBs may be preferential as antihypertensive agents in people living with gout and hypertension.

3. ARBs have a similar evidence base to ACEis but do not cause dry cough

RAASis are foundational therapies for people living with hypertension, CKD, and HFrEF and have been demonstrated to reduce the risk of major adverse CV and kidney outcomes.[10]

ACEis are commonly chosen as first-line RAASis for these conditions. However, incidence of dry cough with ACEis has been as high as 30% in some studies,[11] and may lead to patient dissatisfaction, reduced compliance, and increased workload in primary care if the switch to an ARB is required.

ARBs also have a well-established evidence base for the above conditions, are generic, and do not cause cough.[11–13] Personally, losartan is my ARB of choice because of its straightforward posology and simple dosing titration schedule (50 mg titrated to 100 mg for most individuals, and 12.5 mg titrated stepwise to a maximum of 150 mg in HFrEF[14]).

For people living with HFrEF, consider directly initiating an ARNI (sacubitril–valsartan) rather than an ACEi/ARB whenever possible, to avoid delays in optimising GRMT.[15–17]

See also the Primary Care Hacks on CKD and HFrEF.

Consider ARBs as first-line therapy when choosing an RAASi for people living with hypertension and/or CKD.

4. Oral iron absorption is most effective with once-daily or alternate-day dosing of supplements

Although iron supplements used to be given up to three times daily, more recent studies have shown that taking one dose each day or on alternate days can help to optimise iron absorption.[18]

Therefore, for first-line treatment of iron deficiency, a single daily tablet is recommended, taken until 3 months after iron deficiency is corrected to allow stores to be replenished.[19] If not tolerated, consider either reducing to alternate-day dosing or switching to an alternative preparation with lower elemental iron content.[19]

Ferrous sulfate (200 mg) is a sensible first choice.[19,20] Standard ferrous fumarate tablets contain more elemental iron (~69 mg) than ferrous sulfate tablets (~65 mg) so are unlikely to be better tolerated; therefore, ferrous gluconate tablets (~35 mg) may be preferrable.[20]

See also the Primary Care Hack on iron studies.

Consider once-daily or alternate-day dosing of iron supplements to optimise absorption and improve compliance.

5. Rosuvastatin is effective and well tolerated at doses as low as 5 mg once weekly

Although statins are largely well tolerated in clinical trials, up to 75% of people in the real world will discontinue statin treatment within 2 years.[21] If side effects are experienced, therefore, it is important that clinicians address patient concerns and take steps to find a treatment regimen they will adhere to.[21]

One pragmatic approach to statin intolerance (reflecting NHS AAC guidance[21]) would be to try two high-potency statins (atorvastatin and rosuvastatin) before moving to nonstatin agents. Because atorvastatin is lipophilic and rosuvastatin is hydrophilic,[22] it would be sensible to try one of these if a patient experiences side effects with the other. Rosuvastatin may be particularly useful in such cases because it can be initiated at doses as low as 5 mg once-weekly and then slowly increased to maximum tolerated doses.[23,24] Alternate-day or twice-weekly dosing can be useful in the first instance, lowering doses to once-weekly if not tolerated.

See also the Primary Care Hack on lipid management.

Consider once-weekly rosuvastatin 5 mg in those with statin intolerance, slowly increased to the maximum tolerated dose.

6. SGLT2is have negligible glucose-lowering effects once eGFR falls below 45 ml/min/1.73 m²

The glucose-lowering efficacy of all SGLT2is is dependent on renal function, and likely absent in severe renal impairment.[25] Therefore, people living with T2D who are taking an SGLT2i may require additional glucose-lowering treatment if their eGFR falls below 45 ml/min/1.73 m².[25]

Certain SGLT2is have beneficial cardiorenal effects at all stages of renal impairment and should be continued anyway. Always review all indications for SGLT2is before making the decision to discontinue.

See also the Primary Care Hack on extra-glycaemic indications of SGLT2is.

If eGFR is <45 ml/min/1.73 m², continue SGLT2is for cardiorenal protection and consider additional glucose-lowering therapy if HbA_{1c} remains above target.

7. Low-dose doxycycline tends to exert anti-inflammatory rather than antibacterial effects

Rosacea is a chronic disorder affecting the facial skin that is commonly encountered in primary care. Its aetiology is largely unknown.[26]

PCDS guidance recommends ivermectin 1% cream as first-line therapy for inflammatory (papular/pustular) rosacea.[26,27] Ivermectin is well tolerated, applied once daily, demonstrates greater efficacy than metronidazole, and is not associated with antibiotic resistance.[26,27]

However, if systemic treatment is required for inflammatory rosacea, the PCDS recommends low-dose doxycycline (40 mg MR od).[26,27] This treatment regimen has demonstrated anti-inflammatory properties and is associated with fewer side effects than full-dose doxycycline (100 mg), with equivalent efficacy.[27,28] This is also a submicrobial dose, reducing the risk of antibiotic resistance.[27]

Consider low-dose doxycycline for the systemic treatment of inflammatory (papular and pustular) rosacea.

8. Topical retinoids, although effective, can cause excessive dryness and skin irritation on initial use

Acne is ubiquitous among adolescents, with around 15% of teenagers seeking treatment for the condition.[29] Topical retinoids are a first-line treatment choice in all stages of acne but can cause excessive dry skin and/or skin irritation on initial use.[29,30]

A short-contact regimen can ameliorate this irritant reaction[29,30]—e.g. by applying a small amount of the retinoid to the skin every 2nd or 3rd day and leaving it on for 30–60 minutes before washing off. The target dose is once-daily application overnight, which can be reached with a gradual build up in frequency and then duration of application.[29,30] Daily use of a noncomedogenic moisturiser may also lessen symptoms.[30]

See also the Primary Care Hack on acne.

To ameliorate irritant reactions, start topical retinoids with a short-contact regimen.

9. Owing to its mechanism of action, gliclazide is preferred for the initial management of glucocorticoid-induced diabetes and hyperglycaemia

It is established that the use of glucocorticoids can cause abnormalities of glucose metabolism by impairing the function of beta cells.[31] These abnormalities are classified as 'glucocorticoid-induced hyperglycaemia' (worsening hyperglycaemia in the context of known diabetes) or 'glucocorticoid-induced diabetes' (hyperglycaemia in the absence of known diabetes).[31]

Because sulfonylureas promote insulin release from pancreatic beta cells, gliclazide is the preferred first-line therapy in this case.[31,32] If a person experiences glucocorticoid-induced diabetes, or glucocorticoid-induced hyperglycaemia in the context of T2D (and they are not taking insulin), a UK consensus recommends:[31]

- gliclazide 40 mg od in the morning, titrated as required to a maximum of 240 mg od
- if glycaemic control is still not achieved: adding an additional evening dose of gliclazide or considering initiation of morning intermediate-acting insulin therapy, directed by CBG readings or CGM.

Note: all people taking gliclazide should have access to SMBG, especially drivers, in view of hypoglycaemia risk.

Also see the Primary Care Hack *What Next After Metformin? Part 1*.

If glucocorticoid use affects glycaemic control, consider commencing gliclazide (40 mg od in the morning) and titrating as required until glycaemic control is achieved.

10. In palliative care, opioids need to be prescribed with care, deliberation, and consideration of appropriate doses of breakthrough pain relief

In palliative care, it is essential that clinicians always prescribe an appropriate drug and dose for breakthrough pain. In most cases, morphine will be the strong opioid of choice.[33,34]

The opioid/opiate conversion tables in the Scottish palliative care guideline can help to guide any switches between opioid medicines.[35] When making any adjustments or switches, it is important to use clinical judgement; further caution is needed for frail and elderly individuals, in kidney or liver impairment, and if opioid toxicity is identified.[35]

It may be appropriate to reduce dose by 30% and retitrate when switching opioids, either because of differences in pharmacokinetics/pharmacodynamics or because the individual is elderly, frail, or opioid toxic.[35] As a general rule, breakthrough pain can be managed with opioid doses of 1/6th–1/10th of the regular 24-hour opioid dose (as required); this would usually need repeating every 2–4 hours, but may happen up to hourly.[33]

When giving opioids, clinicians should also consider prescribing a regular laxative and counsel patients and carers about the risk of constipation.[33] A combination of stimulant and osmotic laxatives is often helpful. Avoid bulk-forming laxatives, as they can exacerbate matters.

In palliative care, calculate opioid doses for breakthrough pain based on a calculation of 1/6th–1/10th of the regular 24-hour opioid dose.

The information in this Primary Care Hack is based on the author's own clinical experience, their interpretation of relevant summaries of product characteristics, and related guidance and evidence.

Abbreviations
AAC=Accelerated Access Collaborative; **ACEi**=angiotensin-converting enzyme inhibitor; **ARB**=angiotensin receptor blocker; **ARNI**=angiotensin receptor/neprilysin inhibitor; **CBG**=capillary blood glucose; **CCB**=calcium channel blocker; **CGM**=continuous glucose monitoring; **CKD**=chronic kidney disease; **CV**=cardiovascular; **eGFR**=estimated glomerular filtration rate; **GRMT**=guideline-recommended medical therapy; **HbA_{1c}**=glycated haemoglobin; **HFrEF**=heart failure with reduced ejection fraction; **MR**=modified release; **od**=once daily; **PCDS**=Primary Care Dermatology Society; **RAASi**=renin–angiotensin–aldosterone system inhibitor; **SGLT2i**=sodium–glucose co-transporter-2 inhibitor; **SBMG**=self-monitoring of blood glucose; **SNRI**=serotonin–norepinephrine reuptake inhibitor; **SSRI**=selective serotonin reuptake inhibitor; **T2D**=type 2 diabetes