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Deprescribing Advanced Therapies in Inflammatory Bowel Disease

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Key Takeaways

- Deprescribing advanced therapies is a viable option for carefully-selected patients living with IBD.
- We propose a systematic approach for deprescribing advanced therapies in IBD, which comprises strategic patient selection, comprehensive risk assessment, shared decision-making, rigorous monitoring, and a pre-defined rescue strategy.
- Further research is needed to improve patient selection tools, optimize monitoring techniques, and clarify deprescribing strategies for newer agents.

Introduction

Deprescribing refers to the systematic process of discontinuing or reducing the dose of a medication under healthcare provider supervision to improve patient outcomes.¹ This concept is increasingly recognized across medical fields as a strategy to minimize medication burden, reduce long-term adverse effects, and improve health-related quality of life.² However, there is minimal guidance on *how* to deprescribe medications, leading to challenges with implementation.³

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is characterized by chronic, relapsing-remitting inflammation of the gastrointestinal tract.⁴ Recently, deprescribing has gained attention in IBD management, particularly given the serious adverse effects and high financial costs associated with prolonged use of advanced therapies.^{5,6} In patients with IBD, the decision to deprescribe requires careful consideration of the serious risk of disease recurrence, and the challenge of recapturing response after relapse.⁷ This review aims to synthesize existing literature on deprescribing advanced therapies in IBD, and to provide a practical framework for deprescribing in this context.

General Approach to Deprescribing

A methodical, risk-stratified approach is fundamental to identifying appropriate candidates for deprescribing in IBD, as not all patients in remission are suitable for medication withdrawal. The process may begin with clinician concerns regarding long-term medication safety (e.g., thiopurine deprescription in the elderly), or with a patient interest in deprescribing due to concerns around risk, medication burden, cost, or personal preference. Prior to deprescribing, patients must understand and accept the risks, desire medication reduction or cessation, and commit to the necessary rigorous monitoring. A comprehensive assessment of both clinical and medication-related factors can help predict the likelihood of relapse following medication withdrawal and identify high-risk candidates who should continue therapy when possible. For patients that opt to proceed with medication reduction or cessation, deprescribing should be performed with close proactive monitoring and a clear plan for reinitiating treatment in the event of a relapse. An algorithmic approach to identifying candidates for deprescribing is presented in **Figure 1**. Each aspect of this stepwise approach is discussed in detail in the subsequent sections.

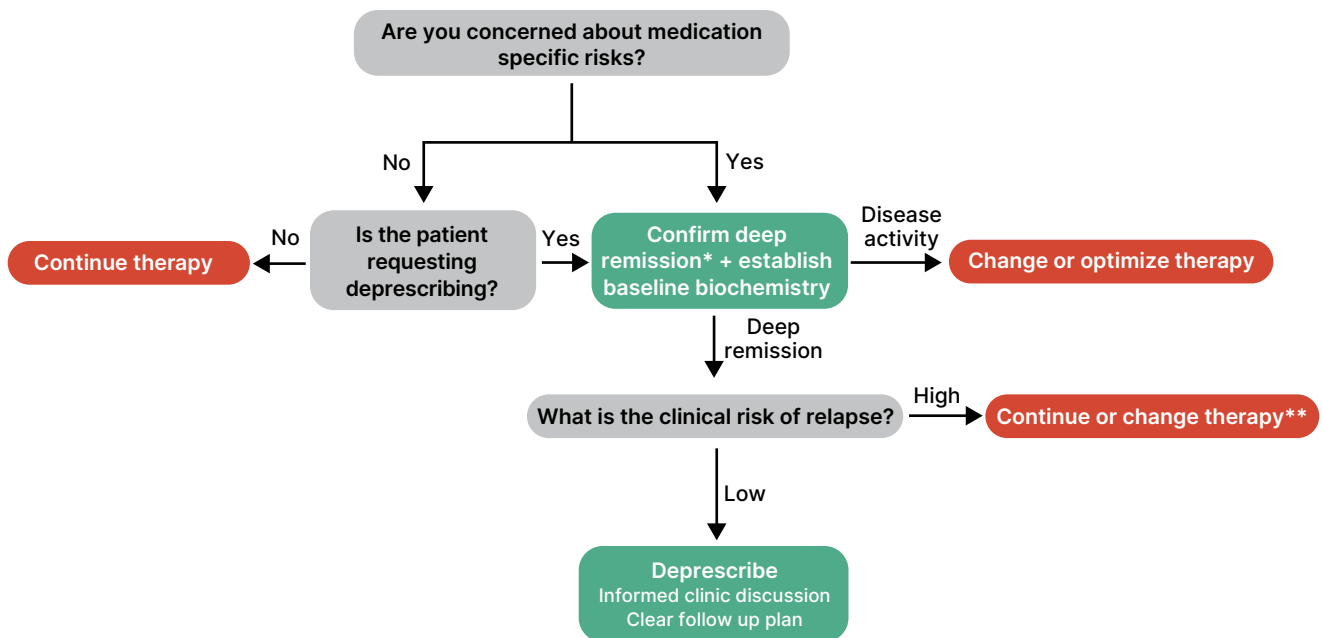


Figure 1. Algorithmic approach to identifying candidates for deprescribing; courtesy of Elizabeth Squirell, MD, MSc, FRCPC, Jason Hearn, MD, MHSc and Mark McMillan, MD, FRCPC, CAGF.

*Deep remission is characterized by endoscopic remission in accessible segments of the GI tract and/or radiographic remission in regions not amenable to endoscopic evaluation, such as the mid small bowel.

**If medication risks prompted consideration of deprescribing but there is a high risk of relapse, consideration should be given to a change in therapy (e.g., azathioprine in older adults).

Communication and Shared Decision-Making

Successful deprescribing in IBD hinges on shared decision-making and transparent communication. Clinicians must clearly articulate the potential advantages (e.g., reduced medication burden and drug-related toxicities) alongside the significant risk of relapse. This discussion should include a quantified estimate of relapse risk and address the possibility of severe relapse requiring hospitalization and/or surgery.⁸ Exploration of patient values and preferences is critical, as some may accept an elevated relapse risk to avoid prolonged pharmacotherapy, whereas others may prioritize sustained disease control. A detailed monitoring plan, including a “rescue strategy” to be used in the event of disease relapse, should be mutually agreed upon prior to drug cessation.⁹ Patients should be reassured that remission can typically be recaptured through prompt initiation of previously-effective therapies.¹⁰

Clinical Predictors of Relapse

Specific clinical factors have been associated with an increased risk of relapse following deprescribing in IBD.⁹ These include younger age (i.e., under 30–40 years),¹¹ male sex,¹² active smoking,¹³ ileocolonic disease location,¹⁴ perianal and/or stricturing phenotypes,¹⁵ and a history of previous IBD surgery.¹⁶ Indicators of active disease at discontinuation are also correlated with an increased risk of relapse, including elevated inflammatory markers (e.g., fecal calprotectin level [FCP], C-reactive protein level [CRP]) and inflammation on endoscopy.¹⁷ A shorter duration of remission prior to deprescribing (i.e., less than 2–4 years) appears to elevate the relapse risk, whereas longer remission is associated with a lower risk.^{12,18} Both histologic remission and transmural healing show promise in relapse prediction.¹⁹ However, there is limited prospective data using these stringent targets to guide treatment withdrawal, as most studies have relied on less strict clinical and endoscopic criteria.

	Thiopurines	Methotrexate	Anti-TNF agents	Other biologics	Small molecules
Adverse effects	Infection, hepatotoxicity, myelotoxicity, melanoma, lymphoma ^{20–23}	Hepatotoxicity, myelosuppression, pneumonitis, gastrointestinal toxicity ²⁵	Infection, melanoma, lymphoma ^{29,30}	Minimal risks ^{33,34}	Malignancy, major adverse cardiovascular events, thrombosis ³⁸
Risk of relapse with medication withdrawal	37% at 18 months ²⁴ No significant effect when removed from combination regimen ²⁷	No specific studies for monotherapy withdrawal No significant effect when removed from combination regimen ²⁷	44% in CD and 38% in UC ³² Similar rates when removed from combination therapy ²⁷	Similar risk to anti-TNF agents ^{35–37}	81% in UC ³⁹
Reasons to consider deprescribing	Serious side effects, older patients, deep remission (i.e., >4 years) ²⁴	Serious side effects	Serious side effects, deep remission ³²	Serious side effects	Serious side effects

Table 1. Summary of deprescribing considerations by class of advanced therapy; courtesy of Elizabeth Squirell, MD, MSc, FRCPC, Jason Hearn, MD, MHSc and Mark McMillan, MD, FRCPC, CAGF.

Abbreviations: CD: Crohn's disease, UC: ulcerative colitis, TNF: tumour necrosis factor

Outcomes by Medication Class

The decision to deprescribe in IBD requires thoughtful consideration of factors specific to each medication class, including the potential adverse effects of continuing treatment and the risk of relapse with drug cessation. Key considerations for each medication class are summarized in **Table 1**.

Immunomodulators

Thiopurines (Azathioprine, 6-MP):

Long-term thiopurine exposure is associated with several dose-dependent risks. Key concerns include serious infections (3–7% annually), a 4-to-6-fold increase in lymphoma risk, and an increased risk of hepatosplenic T-cell lymphoma.^{20,21} Additionally, thiopurine treatment is a risk factor for non-melanoma skin cancer, with hazard ratios of 5.9 and 3.9 for ongoing treatment and past exposure, respectively.²² Other potential adverse effects include hepatotoxicity and myelosuppression.²³ It is important to note that several of these risks—such as lymphoma and non-melanoma skin cancer—are significantly higher in elderly patients.^{20,22} Encouragingly, the elevated lymphoma risk appears to return to

age-related baseline levels after the medication is discontinued.²⁰

Deprescription of thiopurine monotherapy has been associated with a significant relapse risk. A meta-analysis demonstrated a significantly increased risk of relapse in patients discontinuing a thiopurine at both 12 (33% versus 15%) and 18 months (37% versus 21%) compared to continued therapy; however, the difference was non-significant at 5 years (78% versus 67%). Longer remission (>4 years) prior to discontinuation was found to be protective.²⁴

Methotrexate: Risks associated with methotrexate include hepatotoxicity with rare fibrosis, myelosuppression, pneumonitis, and gastrointestinal toxicity.²⁵ Serious infections and malignancies are not commonly associated with methotrexate. Though high rates of discontinuation due to poor tolerance are observed,²⁶ no formal withdrawal studies relating to methotrexate monotherapy could be identified. In women considering pregnancy, methotrexate should be routinely changed to a non-teratogenic therapy offering comparable effectiveness.

Combination therapy: Both thiopurines and methotrexate are used in combination with anti-TNF agents. The SPARE trial, which assessed medication withdrawal in stable CD patients on combination regimens, showed that

immunomodulator discontinuation (i.e., reduction to anti-TNF monotherapy) yielded statistically equivalent relapse rates at 2 years (10%) compared to continued combination therapy (12%).²⁷ As such, immunomodulator deprescription should be considered in patients with CD who are in deep remission while on combination therapy.

Biologics

Anti-Tumour Necrosis Factor (TNF):

Long-term adverse effects of anti-TNF therapy include serious infections (3–5% annually), a modest 1.5-fold increased risk of melanoma, and rare paradoxical immune-mediated reactions.^{28,29} While lymphoma risk is minimal with monotherapy, it increases when combined with an immunomodulator. Combination therapy is associated with a 100-to-1000-fold increase in hepatosplenic T-cell lymphoma, particularly in young males (affecting ~1/7400).³⁰ Additionally, anti-TNF agents are contraindicated in patients with severe heart failure.³¹

Deprescribing anti-TNF agents is associated with a consistently high risk of relapse following medication withdrawal. A 2015 systematic review including 27 studies of anti-TNF withdrawal identified an overall risk of relapse of 44% in CD and 38% in UC. Notably, remission was successfully reintroduced in 80% of cases using the same anti-TNF agent.³² Similarly, the SPARE trial, which investigated the withdrawal of anti-TNF agents in stable patients with CD on a combination regimen of anti-TNF and an immunomodulator, found that anti-TNF cessation resulted in a substantially higher relapse rate at 2 years (36%) compared to continued combination therapy (12%).²⁷ It is important to note that medication withdrawal studies to date have enrolled patients in clinical remission without the requirement for endoscopic healing. Subgroup analyses suggest that mucosal healing before deprescription is associated with a lower relapse rate of 26%.³² Based on this evidence, cessation of anti-TNF agents should only be considered for patients in deep remission, including endoscopic healing, or in those experiencing severe adverse effects and/or expressing a significant interest in deprescribing.

Other Biologics: Vedolizumab and ustekinumab have favourable safety profiles with no documented increase in serious infections or malignancies, though vedolizumab is linked to a higher rate of nasopharyngitis.^{33,34} Although deprescribing data are less extensive for these

agents, available evidence suggests a high relapse rate. One multicentre cohort study of vedolizumab withdrawal has shown a relapse rate of 64% within one year, with retreatment success in 63% of relapsed patients.³⁵ Ustekinumab withdrawal remains insufficiently studied, though recent studies suggest relapse rates are likely similar to those seen with anti-TNF cessation.^{36,37} Given the safety profile and high likelihood of relapse with discontinuing vedolizumab or ustekinumab, very few patients stand to benefit from deprescribing these agents. Despite similar safety profiles, the withdrawal of newer biologics, such as IL-23 inhibitors, has not yet been studied.

Small molecules

Janus kinase (JAK) inhibitors have established safety concerns, most notably increased risks of infectious complications, malignancies, major adverse cardiovascular events, and thromboembolism.³⁸ Despite these potential risks, withdrawal evidence is minimal for these agents. A recent multicentre cohort study investigated outcomes for JAK inhibitor withdrawal amongst patients with stable UC, and found a dramatically increased risk of relapse (81% versus 8%) and shorter duration of mean relapse-free survival (882 days versus 1679 days) for patients who discontinued versus continued the medication. Notably, reinduction using JAK inhibitors was successful in 83% of relapsed patients.³⁹ Studies on the withdrawal of other small molecules, such as S1P receptor modulators, are currently lacking. Given the limited available evidence, it is difficult to make a recommendation on deprescribing small molecules in the absence of severe adverse effects. If deprescribing is considered, the same general principles described above should be adopted.

Monitoring Strategies After Deprescribing

Intensive proactive monitoring is *essential* for the early detection of relapse to allow prompt initiation of therapies, minimize flare severity and complications, and increase the likelihood of successful reinduction. Structured follow-up assessments should be undertaken quarterly during the first year, and patients should be counselled to seek medical attention if signs of disease relapse develop.⁸

Biomarker surveillance also allows early identification of relapse, even in asymptomatic individuals, as elevated FCP levels have been shown to precede clinically apparent relapse.⁴⁰ An optimal monitoring protocol includes measuring FCP and/or CRP at three-month intervals during the first year, with more frequent testing when clinically warranted.⁴¹ FCP levels between 100 and 250 µg/g should prompt closer monitoring or holistic assessment, while levels above 250 µg/g suggest active inflammation warranting endoscopic assessment or consideration of therapy reinitiation.⁴²

While mucosal healing should be confirmed prior to deprescription, the value of routine endoscopic surveillance after deprescribing remains debated. Some experts recommend routine colonoscopy within 6–12 months following medication withdrawal, particularly for patients at high risk of relapse.⁴¹ Others prefer a reactive approach with endoscopic evaluation only when symptoms or biomarkers suggest relapse.⁷ Given the variance in clinical practice, the approach to endoscopy should be individualized based on risk assessments and patient preferences.

Cross-sectional imaging techniques such as magnetic resonance enterography and intestinal ultrasound are non-invasive options to assess inflammation,⁴³ and are well suited for monitoring after deprescribing given their minimal risk profile.

Future Directions

Despite the expanding interest in deprescribing strategies, substantial knowledge gaps persist that necessitate dedicated research. Many foundational deprescription studies have primarily included patients in *clinical* remission; thus, the impact of initial endoscopic or histologic remission on relapse rates requires further study. Similarly, no definitive consensus has emerged regarding the requisite duration of remission prior to medication withdrawal. Comprehensive longitudinal data are also required to evaluate the impact of deprescribing on disease trajectory, disease complications, and health-related quality of life. Non-invasive imaging techniques, such as intestinal ultrasound, warrant further consideration as monitoring options of disease activity following drug cessation. Finally, the evidence regarding the deprescribing of newer therapeutic agents remains particularly scarce, underscoring the need for further study.

Conclusion

Deprescribing advanced therapies in IBD remains a complex decision. While not suitable for routine practice due to significant relapse risks, it is a viable option for carefully-selected individuals. We present a stepwise approach to deprescribing in this context.

- First, proactively **identify candidates** for deprescribing by focusing on those with confirmed endoscopic remission for a prolonged period (i.e., greater than 2–4 years), especially if the patient is motivated or facing risks associated with extended drug exposure.
- Second, perform a **systematic risk assessment** based on patient history, recent biomarkers of inflammation, and the depth of remission to inform counselling.
- Third, implement robust **shared decision-making** by quantifying relapse risks, discussing the high rates of successful response recapture in the event of relapse, and confirming the patient's understanding and explicit acceptance of risk.
- Fourth, use **medication-specific strategies**, such as considering thiopurine cessation in patients over 60 years or with prolonged drug exposure.
- Fifth, establish a **concrete monitoring plan** before cessation, including regular reviews and biomarker testing with clear thresholds for action.
- Finally, develop a pre-defined **"rescue plan"** for managing potential relapse, typically involving prompt reinitiation of therapy.

While current evidence provides a framework, further research to refine patient selection tools, optimize monitoring techniques, and clarify strategies for newer agents is crucial for enhancing the safety and success of deprescribing in IBD clinical practice.

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