

Common Counselling Points:

FACT OR FICTION

Below are some common statements made in counselling that we decided to check if the evidence supports. Full explanations follow.

#1: Penicillin V Should Be Taken on an Empty Stomach – **FACT**

Absorption is significantly impacted by food, and absorption is maximized in a fasting state.

#2: Metronidazole + Ethanol = Disulfiram Reaction – **UNCERTAIN**

While evidence suggests this interaction does not exist, the data available is not robust enough to disprove the claim. It is prudent to inform patients of potential harm when alcohol is combined with metronidazole and encourage cautious use of alcohol in those who decide to combine; however, there are no grounds to consider the combination contraindicated.

#3: Tramadol is less addictive than other opioids - **FACT BUT...**

Based on the Canadian scheduling of tramadol in the Prescription Drug List as opposed to the Controlled Drugs and Substances Act, there may be a perception of an absence of abuse potential. However, abuse potential is present and needs to be counselled for accordingly.

#4: Common Antibiotics Decrease Efficacy of Hormonal Contraception – **FICTION**

Patients have attributed contraceptive failure to an interaction between antibiotics and hormonal contraception. Contraceptive failure is known to occur with typical use of hormonal contraception. Since antibiotics are commonly prescribed, there are going to be cases of women experiencing contraceptive failure around the time of taking an antibiotic; the evidence suggests this is correlation, not causality. With the exception of rifampin, antibiotics do not affect the concentrations of estrogens or progestins from hormonal contraceptives. Severe GI symptoms that may be caused by antibiotics, may affect the efficacy of oral contraceptives due to decreased absorption.

#5: A Penicillin Allergy Lasts a Lifetime – **FICTION**

Evidence shows that most people who list penicillin as an allergy fail to react to an allergic skin test. An 80% spontaneous resolution rate within a decade of the last exposure has been documented.

#1: Penicillin V Should Be Taken on an Empty Stomach – **FACT**

Penicillin is a medication that was discovered in 1928 by Alexander Fleming,¹ so recent studies of the molecule are lacking. A study completed by McCracken et al. in 1978 reviewed salivary and serum penicillin levels following administration of penicillin V and G orally to infants and children. When these were administered with milk there was noted decrease in peak plasma concentrations and AUC, which can perpetuate treatment failure.² Another study by Finkel et al. published in 1981 assessed the effect of food on absorption of penicillin V when given to children before, with, or 2 hours after meals. Results consistently showed that the extent of absorption was directly affected by food intake, with best absorption occurring on an empty stomach at least 2 hours after food.³ References differ in their recommendations on administration of penicillin. The manufacturer states that it may be taken with food without loss of efficacy,⁴ Lexicomp and AHFS both recommend taking penicillin V on an empty stomach at least one hour before or two hours after food.^{5,6} Lexicomp does provide the recommendation that in pediatric patients it may be taken with food to minimize GI side effects.⁵ There is a lack of data on clinical outcomes with this recommendation in pediatric patients and no data in adults.

#2: Metronidazole + Ethanol = Disulfiram Reaction – **UNCERTAIN**

Disulfiram is an aldehyde dehydrogenase inhibitor that when combined with alcohol leads to a dose-dependent reaction affecting the cardiovascular, pulmonary and gastrointestinal systems. This reaction led to the development and marketing of disulfiram as a medication to manage alcohol use disorder.⁷ Metronidazole is a commonly used antibiotic that has been hypothesized to perpetuate a similar reaction with alcohol, but the mechanism is unknown.⁸ This interaction is listed in the drug product monograph, but no supporting research is provided.⁹ A study conducted in rats failed to show alcohol dehydrogenase inhibition or elevated serum acetaldehyde levels.¹⁰ Despite case reports noting this interaction, small studies and literature reviews have failed to show a significant interaction between alcohol and metronidazole.^{11,12} In all of the published case reports, the cause of symptoms was noted to be the well-accepted interaction between alcohol and metronidazole, so further investigations were not completed.¹³ Despite its prevalence in professional databases,^{12,14} this reaction is not well documented, and the existence has been questioned in one review of case reports.¹³ It has been suggested that the symptoms seen in these cases are related to symptoms of illness, side effects of metronidazole or alcohol intoxication, and not from a drug interaction as previously believed.^{12,13} Although evidence fails to confirm this interaction, the general recommendation to avoid the combination remains prevalent.^{8,9,12,14} Although the evidence is weak, it is strongly recommended to discuss possible risks with patients if they choose to combine alcohol with metronidazole.¹²⁻¹⁴

#3: Tramadol is less addictive than other opioids - **FACT BUT...**

Tramadol is an analgesic with two main mechanisms of action: the first is modulation of adrenergic and noradrenergic receptors (i.e. serotonin and norepinephrine); the second is as an opioid agonist after the prodrug is converted via CYP 2D6 metabolism.¹⁵

The World Health Organization's (WHO) Expert Committee on Drug Dependence has reviewed tramadol and its abuse potential periodically since 1992. Throughout the years, the committee has concluded abuse potential to be low such that international control was not warranted.¹⁶ Canadian,¹⁷ American¹⁸ and UK¹⁹ regulatory agencies have regulated tramadol less stringently than other opioids; however, tramadol is considered a controlled substance in the USA and

UK, but not in Canada. These agencies base decisions of classification in part on a drug's perceived or real abuse potential, suggesting dissention regarding the abuse potential of tramadol.

Epidemiological and postmarketing surveillance have reported low abuse and diversion since tramadol was introduced into the US in 1994.²⁰⁻²⁴ While direct comparative data of tramadol's abuse potential are sparse, weak evidence suggests tramadol has lower abuse/dependence potential than buprenorphine²⁵ and hydromorphone.²⁶ However, studies have demonstrated tramadol to elicit effects of abuse liability such as "likeability",²⁷ "wanting to take again",²⁷ and "similarity to previous opioid experience"²⁸ in drug users. Furthermore, tramadol activates reward pathways in healthy volunteers as seen with functional magnetic resonance imaging.²⁹

An interesting consideration is that observational data includes single-ingredient and combination tramadol products. The second agent in the combination products (usually acetaminophen) may limit the dose escalation and morbidity commonly seen in opioid use disorder. It's possible (but unsubstantiated) that if observational data were contained to tramadol-only products, abuse prevalence that is similar to other opioids may emerge. This could mask the true abuse prevalence of tramadol-only products.

Tramadol does have potential for abuse. This risk may be less than other opioids, but reliable data is lacking. It is prudent to apply the same safe prescribing and dispensing principles with respect to abuse and addiction potential used for other opioids to tramadol.

#4: Common Antibiotics Decrease Efficacy of Hormonal Contraception – FICTION

This myth has some truth to it, as rifampin and related antibiotics do cause hormonal contraceptives to become less effective through enzymatic induction.^{30,31} However, this does not translate to all antibiotics having a negative effect on hormonal contraceptives.

The use of common antibiotics in practice is not associated with a decrease in the efficacy of hormonal contraception.³⁰⁻³⁵ Despite case reports of patients experiencing contraceptive failure while on antibiotics, studies conducted show no difference in rates of pregnancy in patients on antibiotics plus hormonal contraceptives vs. patients on hormonal contraceptives alone.^{33,34} These case reports can likely be explained by the failure rate of oral contraceptives with typical use, which may be as high as 9% in the first year.³¹ Monographs of many hormonal contraceptives warn about this interaction, further convoluting this issue for patients.^{30,31}

Vomiting or diarrhea, which may be associated with illness or antibiotic use, potentially decreases absorption of oral contraceptives; however data supporting this is sparse as oral contraceptives are rapidly absorbed.^{31,36} Nevertheless, considering the implications of contraception failure, it is prudent to advise patients of the risk of reduced absorption of oral contraceptives if they experience severe diarrhea lasting longer than 24 hours or vomiting within 3 hours of taking their oral contraceptive. This situation can be managed by following a missed pill protocol and/or using back-up contraception (e.g. condoms) or abstinence during and for at least 7 days following the diarrhea/vomiting.³¹ For patients using non-oral forms of contraception, diarrhea and vomiting do not have a pronounced effect.³¹

#5: A Penicillin Allergy Lasts a Lifetime – FICTION

Up to 10% of the population lists penicillin as an allergy, but up to 95% of these individuals are not truly allergic.^{37,38} True frequency of anaphylaxis is estimated at between 1 and 5 per 10,000 courses of penicillin.³⁹

Many people believe that if they react poorly to a penicillin (either an allergy or intolerance) they need to avoid further courses. This may be true if a patient has experienced an IgE mediated reaction, which can be confirmed via skin sensitivity testing. When documenting a penicillin allergy it is important to clarify the type of reaction, as well as how long ago it occurred. If a patient describes a distant memory of an allergy as a child, it is likely not appropriate to label them as penicillin allergic.^{37,38,40} Application of this erroneous beta-lactam allergy label affects the types of antibiotics that may be prescribed, which may lead to use of broad-spectrum agents that cause increased antibiotic resistance.^{37,39} It is very common that clinicians will label a patient penicillin allergic based on self-reported reactions, with little or no details of the reaction.³⁷

It is recommended that in a presumed allergy, allergic skin testing be done to confirm whether an IgE mediated allergy is present. Referral to an allergy specialist may be warranted to rule out a true immune-mediated reaction, as reliable tests are not commercially available.^{37,39} Literature shows that up to 90% of people with a stated penicillin allergy do not form a reaction to a penicillin skin test.^{37,40} In cases where a patient tests positive on a skin test, it is important to conduct follow up testing, as spontaneous resolution occurs in 50% and 80% of patients at 5 and 10 years, respectively.^{38,41} This means that patients with a distant history of an allergy are likely no longer allergic, but should undergo skin testing to confirm, especially when the reaction was severe.

If a patient has a positive reaction to a skin test and has an infection for which there is no reasonable alternative, desensitization therapy is an appropriate clinical approach.^{37,41} Desensitization involves introducing small amounts of the allergen in a controlled environment, and slowly increasing the dose at pre-specified intervals. Desensitization to penicillin is short-lived, as once penicillin doses are missed or stopped, the patient will become sensitized again.^{37,42}

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