GENERAL PHARMACOLOGY

SOURCES OF DRUGS

I. Natural:

- **Plants**
  - * Alkaloids
  - * Glycosides
  - * Fixed oils
  - * Volatile oils
  - * Tannins
  - * Resins
- **Animals**
  - e.g. hormones, vaccines, vitamin D & heparin.
- **Micro-organisms**
  - e.g. antibiotics as penicillin
- **Minerals** as Fe, Ca, I_2, acids & antacids.

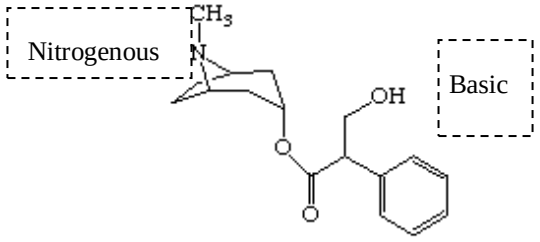
II. Synthetic:

a) Chemical synthesis e.g. salicylates

b) Biological synthesis by Recombinant DNA Technology e.g. human insulin.

Alkaloids

Basic organic nitrogenous compounds of plant origin. Now, they are synthesized. Their names end with "ine" e.g. **atropine**, morphine. They have the following characters:

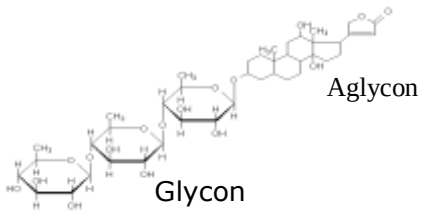


Atropine

1. They are insoluble in water but their salts are soluble, so their salts are the form used clinically
2. They are precipitated by alkali & tannins. Heavy tea may be used in treatment of their toxicity
3. They can cause death without anatomical lesions

Glycosides

Ether-like combinations between sugar (glycon) & non-sugar (aglycon). Their name end with "in" e.g. **digitalis glycosides** (e.g. digoxin)**,** salicin. Glycosides -unlike alkaloids- are soluble in water. They are destroyed by boiling to release the sugar moiety.



Fixed Oils

They are oils of long chain fatty acids. They are mainly used as:

1. Purgative e.g. **caster oil**.
2. Emollient (for skin) & Demulcent (for mucous membrane) e.g. **olive oil**
3. Edible (for cooking) e.g. **sunflower oil**

Volatile Oils

They contain volatile groups. They are mainly used as:

1. Expectorant e.g. **balsam of tolu**
2. Local anaesthetic e.g. **oil of cloves**
3. Irritant, counterirritant e.g. **camphor oil**
4. Carminative & spasmolytic e.g. **peppermint oil**

Tannins

They are precipitating agents.

5. Precipitate surface proteins (Astringent action) → used for diarrhoea.
6. Precipitate alkaloids & iron → used in alkaloid & iron toxicity.
7. They can be obtained on house-hold basis from "heavy tea".

Resins

They are polymerization products of volatile oils e.g. podophylline resin (used in warts).

ROUTES OF ADMINISTRATION

I- ENTERAL route

1. Oral Route

Advantages:

It is the most important method of administering drugs: easy, need no skill or sterilization i.e. self-medication, economic, convenient and acceptable by most patients. The oral dosage forms are usually stable on storage.

Disadvantages:

1) It has delayed onset since gastric emptying takes 2-3 hrs.
2) Variable bioavailability: depends on the extent of absorption & first pass effect.
3) It is not suitable for all types of drugs (e.g. those destroyed in gut as insulin or those irritant to stomach).

It is better to be avoided in:

1)Emergency
2)Convulsion
3)Vomiting

Oral dosage forms:

1. LIQUIDS:

A) SOLUTIONS

Aqueous Solutions:

Water: aqueous solution of volatile oil e.g. peppermint water
Syrup: sugar-saturated aqueous solution e.g. cough syrups
Extract: highly concentrated solution so it is taken as drops

Alcoholic Solutions

Spirit: alcoholic solution of volatile oil e.g. peppermint spirit
Elixir: sweetened hydro-alcoholic solution of the drug e.g. antihistaminic elixirs
Tincture: 10% concentrated drug extract in alcohol e.g. tincture of opium

B) SUSPENSIONS

Mixtures : suspension of solid in water e.g. anti-diarrhea mixtures. It may be sold as a powder for suspension just before use.

Emulsion: suspension of oil in water

2. SOLID:

I. TABLETS

A drug compressed with inert binder.

i) Ordinary tab
ii) Scored tab
iii) Coated tab
iv) Effervescent tab
v) Enteric coated tab
vi) Sustained release tab

II. CAPSULES

A drug enclosed in a gelatin capsule.

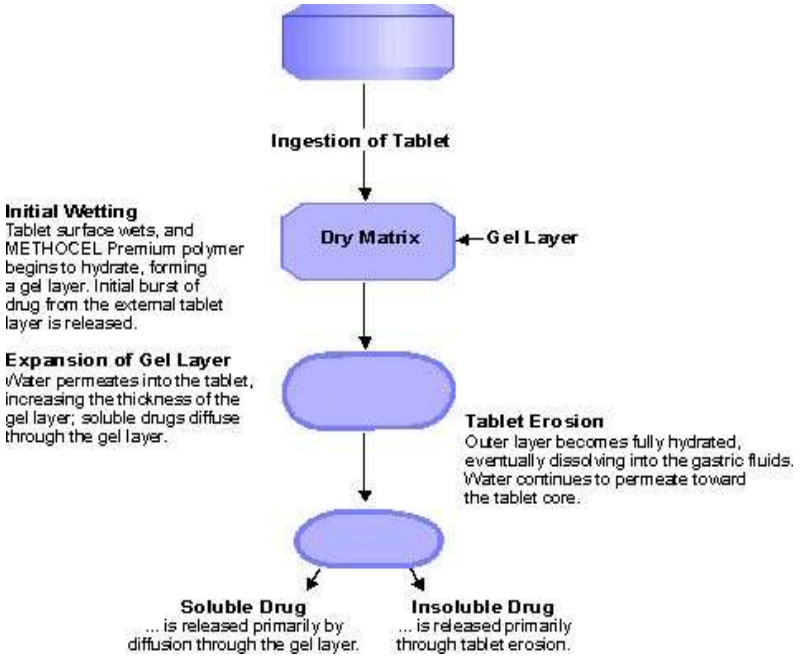
i) Hard gelatin capsule
ii) Soft gelatin capsule
iii) Spansule
iv) Enteric coated capsule: to protect the drug from gastric HCl

There are many types to prepare sustained release tablets:

1. Compressed-release tablets: differential compression of various layers of the tablets allows the outer less compressed layer to release its contents before the inner highly compressed layers.
2. Repeat-action tablets: provides an initial drug dose in the outer layer or shell that rapidly disintegrates in the stomach while the inner layer is insoluble in gastric media but soluble in the intestine.
3. Controlled-release tablets: The absorption rate can be controlled by coating drug particles with wax, by embedding the drug in a matrix from which it is released slowly during transit through the gastrointestinal tract, or by complexing the drug with ion exchange resins (see figure below).

The oral dosage forms contain many substances (excipients) beside the drug itself:

- **Surfactant** increases the dissolution rate by increasing the wet ability,
- **Diluents** increases solubility of the drug. Common diluents include kaolin, lactose, mannitol, starch, powdered sugar,
- **Binder** are added to ease the compaction of tablets. Common binding agent includes cornstarch, glucose, molasses, and various natural gums such as acacia and cellulose derivatives such as methylcellulose**.**
- **Disintegrants**: are added to facilitate tablet disintegration when in contact with water in the gastrointestinal tract.
- **Flavouring** agents and artificial sweeteners such as aspartam and saccharin are usually limited to chewable tablets



Some instructions before oral use:

Taken before meals: This means about one hour before a meal and NOT two minutes before. This may be essential if rapid onset of action is desired or if the drug interacts with food. If the patients has just eat; he may wait for 2 hours after eating to take the drug.

Taken after meals: This applies with irritant drugs to minimize anorexia & nausea. The drug should be taken within five to ten minutes after meals. Some drugs are better absorbed with meals e.g. the antifungal griseofulvin

Taken with water: Instructions to take with water means a full glass of water. This will prevent tablets or capsules sticking into your throat e.g. bran or from damaging the esophagus e.g. bisphosphonates.

To be swallowed whole, not chewed: Enteric coated tablets or capsules have to by pass the stomach since they are acid labile. The coating then dissolves in the intestine to release the medicine where it can best be absorbed e.g. proton pump inhibitors. Sustained release preparation should not be chewed or broken.

2. Buccal Route

1) For local effects:

- **Lozenges**: may be used for local effect.
- **Gargles:** e.g. mouth washes
- **Oral gel:** e.g. antifungal preparations
- **Paste: e.g.** dental paste

2) For systemic effects: sublingual tablets & oral spray:
e.g. nitroglycerine & human growth hormone

Advantages:

- No first pass hepatic metabolism.
- Rapid onset in emergency

3. Rectal route

Indications:

- To produce a local action: e.g. as anti-inflammatory & anesthetic effect for haemorrhoidal conditions.
- To facilitate emptying of the lower bowel e.g. glycerine suppositories.
- To produce a systemic effect. e.g. in fevers, asthma, bacterial infections

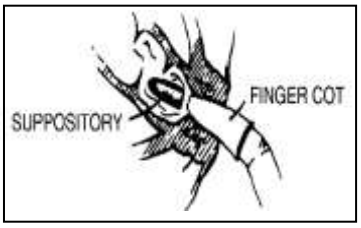
Advantages of rectal route:

- Suitable for children, in presence of vomiting & in comatose pt.

- ❖ Suitable for irritant drugs e.g aminophylline.
- ❖ Prompt onset & prolonged duration of action.

Disadvantages of rectal route:

- ❖ Irregular bioavailability
- ❖ Disagreeable
- ❖ Proctatitis



Dosage forms given per rectum

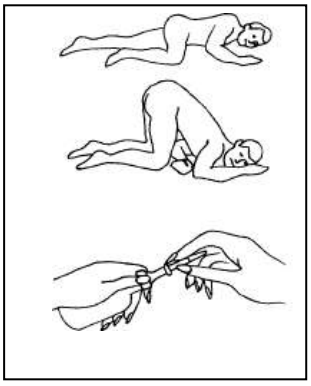
1. Suppositories

2. Enemata (bag or bottle)

How to use rectal suppository:

- o If necessary, go to the toilet to empty your bowels.
- o Either squat or lie on your side with one leg straight and the other bent.
- o Gently but firmly push the suppository, tapered end first, into the rectum (back passage). Push far enough so that it does not slip
- o Close your leg and sit still for a few minutes. Avoid emptying the bowels for at least one hour (unless a laxative suppository)

How to give the enema:



- o As in suppositories
- o Position: leaning forward or on the left side as in suppositories
- o With steady pressure, gently insert enema tip in rectum, with tip pointing toward your navel.
- o Squeeze bottle (or elevate the bag) until nearly all liquid is expelled. High pressure is applied if the aim is to empty the colon but gentle pressure if the drug is to be retained
- o Remove tip from rectum and avoid emptying the rectum for at least 1 hour.

II- PARENTERAL

This form of administration ensures complete bioavailability & rapid onset of action. However, the technique needs sterilization and self-administration is difficult in most of the cases.

Dosage forms

1. LIQUID (INJECTIONS):

Vials

Ampoules

Routes of injections:

1. Intravenous route e.g. theophylline, saline

Precautions during administration:

- Be sure of the dose since the drug can not be retrieved and given under strict aseptic technique.
- Gradual administration and well diluted to avoid phlebitis.
- Strictly intravenous to avoid tissue necrosis.
- Be sure the site of administration is below the level of the heart to avoid air embolism.

Advantages of IV route:

- - Immediate onset (emergency).
- - 100% bioavailability à highly predictable blood levels.
- - Suitable for irritant drugs & for large volumes.

Disadvantages of IV:

- - Extravasations outside the vein →local necrosis.
- - Prolonged infusion → thrombosis.
- - Infection of IV catheter → bacteraemia & phlebitis.
- - Wrong technique → air embolism.

2. Intramuscular route e.g. benzathine penicillin,

Advantages of IM:

- ☒ Rapid absorption
- ☒ Suitable for depot preparation
- ☒ 100% bioavailability

Disadvantages of IM:

- ☒ Unsuitable for large volumes (>5 ml) & irritant drugs
- ☒ Inadvert IVI may occur May be painful
- ☒ May produce infected abscesses

3. Subcutaneous e.g. heparin, adrenaline and insulin

Advantages:

- Uniform absorption
- Prolonged duration of action
- Allows somewhat large volumes

Other methods of injection

Intrarticular injection e.g. corticosteroid
Epidural injection e.g. opioid
Intrathecal or subarachinoid e.g. local anaesthesia

SOLID (IMPLANTS):
e.g. contraceptive pellets

III- INHALATION

Inhalation is an indispensable part in the standard treatment of acute and chronic diseases of the respiratory tract especially obstructive lung diseases e.g. bronchial asthma, chronic bronchitis and emphysema. The medication can be directed to the source of the disease without detouring through the gastro-intestinal tract. Thereby, side-effects of the medication are reduced, and in comparison to other means of treatment, only a fraction of the dosage is required. However, it needs cooperative patient & may lead to respiratory irritation.

A number of factors that influence the availability of inhaled drugs include:

- extent of airway inflammation
- degree of lung metabolism
- amount of drug swallowed and metabolized in the gastrointestinal tract
- patient's ability to coordinate the release and inspiration of the medication
- type of drugs used
- delivery system used

Respiratory dosage forms

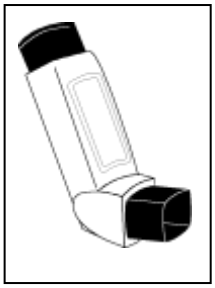
1. **GASES**: e.g. nitrous oxide (given during inhalation anesthesia) and oxygen

2. **VAPOURS**:
   i) Highly volatile (e.g. amyl nitrite and ether)
   ii) Less or Non volatile: these liquids need to be evaporated before use either by boiling e.g. "Tincture Benzoin Co" or by venting with another gas e.g. halogenated anesthetics.

3. **AEROSOLS:**
   Aerosols are suspension of a liquid or solid in a gas.

There are 3 types of inhalers available:

Metered dose inhalers (MDI) are small, portable devices that deliver medication in an aerosol form. They consist of a pressurized canister with a metering valve containing active drugs, low vapor pressure chloroflorocarbon (CFC) propellants, co-solvents and / or surfactants. The canister fits into a plastic device, the mouth-piece, which releases a set amount of medication, or a metered dose.

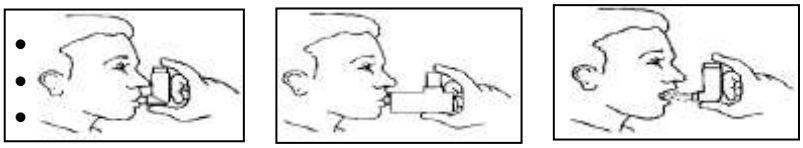


MDI is usually combined with a spacer or a holding chamber to have better compliance for patients with poor hand-lung coordination such as the elderly and children. Advantages of using spacers with an MDI are decreased oropharyngeal deposition and enhanced lung delivery. The purpose of a spacer is to allow evaporation of the propellant prior to inhalation. This allows inhalation after actuation of the devices, obviating the need for good hand-lung coordination and for a greater number of drug particles to achieve a respirable droplet size.

Additionally, most of the large particles that would normally deposit in the oropharynx rain out in the spacer. This will reduce the local adverse effect (hoarseness, thrush).

How to use an MDI correctly:

- Remove cap from the mouthpiece. Shake the inhaler well to mix the medicine.
- There are 3 methods to use an MDI:



- Method 1: Put the mouthpiece of the inhaler in your mouth. Do not block the opening of the mouthpiece with your teeth or tongue.
- Method 2: Connect the spacer (or holding chamber) to mouth & close your lips loosely around the other end of the chamber.
- Method 3: Hold the inhaler 1-2 inches in front of your mouth (about 2-3 finger widths).

1. Exhale (breathe out) slowly all the way.
2. Firmly press down on the inhaler as you inhale (breathe in) slowly. This gives you one dose of medicine. Press your inhaler only 1 time while you are breathing in. If you use a holding chamber, first press down on the inhaler and within 5 seconds, begin to breathe in slowly.
3. Take the mouthpiece away from your mouth. Hold your breath as you count to 10 slowly, if you can. This lets the medicine reach deeply into your lungs.
4. Exhale slowly. Never exhale through the mouthpiece.
5. If you need to take 2 doses, wait 1 minute before the next dose. Do not forget to shake the container.

Dry powder inhalers are used to inhale dry micronized powders directly into the lung. They are activated by the inspiration of the user. They require a forceful inhalation.

- The Rotahaler (e.g. ventolin) requires a capsule of medication (Rotacap) to be placed in the back of the device. The device is twisted to open the capsules and release the medication .
- The Spinhaler (e.g. intal containing cromolyn sodium) is similar to rotahaler; but the deep inspiration leads to spinning of a fan which opens the medication (Spincap) & release the medication .
- The Turbohaler (e.g. maxair autohaler containing pirbuterol) and Diskhaler (e.g. discus adavir containing salmeterol + fluticasone) are multidose devices which require loading a dose prior to inhalation by twisting the grip and puncturing a blister of medication.

Nebulizers: Two types of nebulizers exist, the jet and the ultrasonic nebulizer. Jet nebulizer delivery depends on air compressor; the air flow to the nebulizer changes the medication solution to a mist. They have the advantage of not requiring significant patient coordination or cooperation other than tidal breathing. They are used to deliver aerosols to hospitalized patients or patients with acute asthma exacerbations presenting to the clinic or emergency room.
Ultrasonic nebulizers depend on ultrasonic waves to vibrate the solution of medication resulting in aerosolization.

IV- Skin:

For local effects the following dosage forms can be used:

1. LIQUIDS: **Lotion** (aqueous) **Liniment** (alcoholic)
The lotion is applied to wet skin lesion and is left to evaporate while liniment needs to be rubbed after application.

2. SEMILIQUID: **Cream** **Ointment** **Gel**
Cream & ointment are emulsions: the ointment is applied to dry skin lesions since it contains excess oil while the cream is applied to semi-wet lesions. The gel has the advantage that it can be spread on large areas.

3. SOLID: **Powder** e.g. talc powder or antifungal powder

For systemic effects the following dosage forms can be used:

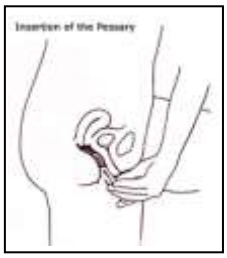
Patches or transdermal delivery system **(TDS)** e.g. fentanyl

Cream or **ointment** e.g.

V- VAGINA :

It is usually used for local effects although systemic effectsmay also occur. Many dosage forms are available:

1. LIQUID (**DOUCHE**): it is usually used for introduction of liquid drugs for local effect e.g. betadine vaginal solution
2. SEMISOLID (**cream**): e.g. estrogen cream and clindamycin cream
3. SOLID (**PESSARY**): e.g. miconazole ovules. The technique of application is shown in the figure.



VI- Eye:

Instruction for application of drugs to the eye:

1. Wash your hands with soap and water before and after use to reduce transmission of microorganism to the eye)
2. If there is crust or discharge, clean the eyelids with a wet a cotton ball with warm water and gently wipe the lid from the inner corner in an outward direction with the eye closed to avoid entrance of microorganisms into the eye.
3. Shake the bottle if it contains a suspension.
4. Open the bottle carefully so that the tip of the eyedropper does not touch anything.
5. Tilt your head back and pull your lower eyelid with the tip of your finger to form a pocket and look up to ease installation of medication and to minimize drainage of medication through the lacrimal duct.
6. Hold the dropper at least 1-2 cm above the eye with the other hand and squeeze the correct number of drops into the pocket

between your lower lid and eyeball without touching the lid with the tip of the bottle.

7. Close your eyes slowly and gently press a finger against the inside corner of each eye and keep them closed for approximately 1 minute to allow the medication to absorb. This helps distribution of medicine evenly whereas squinting or squeezing of eyelids forces medicine out from conjunctival sac.
8. After using the eye drop, do not rinse or wipe the dropper. Keep the bottle clean and tightly closed when you are not using it.
9. When using multiple medications, wait for a few minutes between each application to ensure the eyes have enough time to absorb.
10. If the doctor prescribed you with a combination of eye drops and ointments, and these medications have to be taken at the same time, always remember to apply the eye drops a few minutes before the eye ointment since the ointment hinders the drops absorption.
11. Discard the eye drops after 4 weeks from the date the bottle had been opened.

VII- Nose

Instruction for application of drugs to the nose:

1. If there is any discharge present, clear the nose by using a clean cloth or tissue. This is important that the discharge does not block the distribution of the medication.
2. Hang your head over the edge and tilt your head back as far as comfortable. These actions are to provide access to nasal sinuses and to allow medication to drain to affected sites.
3. Breathe through your mouth to prevent the aspiration of nasal drops into trachea and lungs
4. Instill prescribed number of drops into the nose.
5. Remain in this position for a few minutes to allow the medication to spread in the nose.
6. In case of applying nasal decongestant to open the Eustachian tube; it is advised to apply it twice: the first

time to open the nasal passages & after 5 minutes to open the Eustachian tube. In such case, the head should be tilted 55º backward & 15 º to the side of the affected ear.

7. Do not apply the nasal decongestant to the both sides of the nose at the same time. Two hours between each application is necessary so as the nasal cycle of opening & closing is not changed

The nose can be used also for systemic indications e.g. Vasopressin, Calcitonin, Gonadotrophin releasing hormone analogues

Prescription Writing

Drug Nomenclature:

1. Chemical name: is the name that describes the chemistry of the drug.
2. Generic name: is name used in the literature.
3. *Brand name:* is the name that appears in the prescription

Prescription Writing:

4. Ordinary prescription: This form is used for most of the drugs. This form is tailored by the physician according to his preferences. The instructions for the dispensing pharmacist are written in English & contain information about the dosage form & strength as well as the quantities to be dispensed. The instructions for the patient are written in Arabic and contain information about how to use the drug & the duration of treatment.
5. Special prescription (for table 2 drugs; drugs with low addiction potential): this prescription is written on a special form obtained from the medical syndicate.
6. Narcotic Prescription (for table 1 drugs; drugs with high addiction potential): this prescription is written on special form from the local heath authorities. It is written in duplicate. The patient & the doctor identities should be clearly declared. The dose is written numerically & alphabetically. It can not be refilled.
7. Over The Counter "OTC" drugs: these are the drugs which are dispensed without a prescription.

AUTONOMIC NERVOUS SYSTEM CURVES

I. ADRENERGIC AGONISTS AND ANTAGONISTS

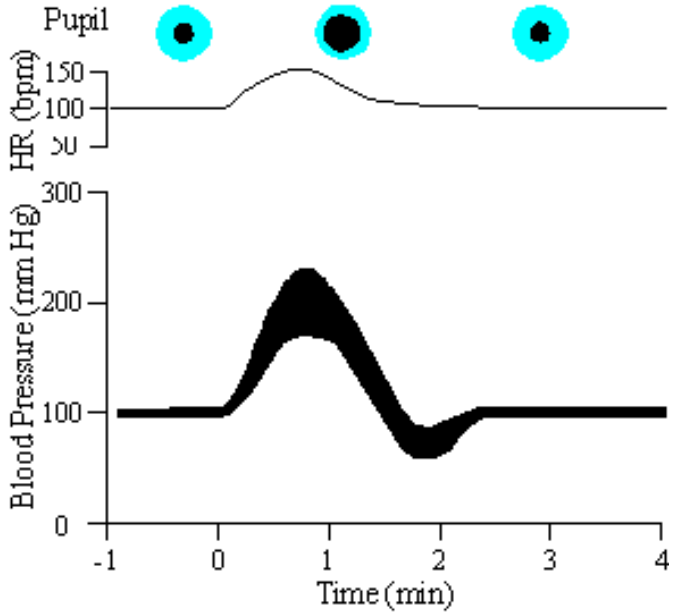
This set of experiments is designed to demonstrate some of the effects of drugs which influence adrenergic receptors in the sympathetic nervous system and its effector organs. Before proceeding, you should have reviewed your lecture notes and/or the text on the Sympathetic Nervous System and adrenergic agonists and antagonists.

We'll start out by describing the experimental arrangement:
An anesthetized cat, prepared for recording arterial blood pressure, is to be given various drugs intravenously in a sequence designed to illustrate site and specificity of drug action. The 2 kg cat was anesthetized with sodium pentobarbital 35 mg/kg IV. This should keep the cat anesthetized for the duration of the demonstration unless you are one of those who works too slowly. If you plan to work with this demonstration for more than 6 hours, be prepared to have this cat wake up on you.

Now, let's go over the experimental setup more carefully:
After the animal was anesthetized, the right femoral triangle was shaved. A 2-inch incision was made, and the femoral vein was exposed by blunt dissection and cannulated. The drugs will be injected by this route. The femoral artery was also exposed, cannulated, and connected to a pressure transducer wired to a polygraph. This allows us to measure the blood pressure and pulse pressure. The heart rate is computed by counting the pen going up and down as blood pressure is being recorded. In this demonstration, we will count the pen movements and calculate the heart rate for you.

The blood pressure tracing should be carefully studied because it will contain increases and decreases in the pulse pressure.

The first drug we will administer is epinephrine bitartrate



The figure shows the responses to 2 µg (base)/kg epinephrine administered intravenously to our instrumented cat.

1. Which of the following is true about epinephrine?
   a. It stimulates α-$_1$ receptors.
   b. It stimulates β-$_1$ receptors.
   c. It stimulates α-$_2$ receptors.
   d. It stimulates β-$_2$ receptors.
   e. All of the above

Foil "e" is correct: epinephrine –unlike noreinehrine- stimulates all adrenoceptors.

2. Factors responsible for the rise in blood pressure include:
   a. Increased myocardial contraction.
   b. Increased heart rate.
   c. Vasoconstriction of the vascular beds.
   d. Vagal reflexes.

Foils "a, b, c" are correct: Vagal reflexes are triggered by the effect of increased BP on baroreceptors and tend to return it back to normal.

3. In this blood pressure tracing, you may have noticed that the effect of epinephrine on blood pressure was quickly

terminated. Which factors may contribute to the rapid termination of the actions of epinephrine?

a. Metabolism by COMT.
b. Metabolism by MAO.
c. Reuptake mechanisms.
d. Metabolism by esterases.

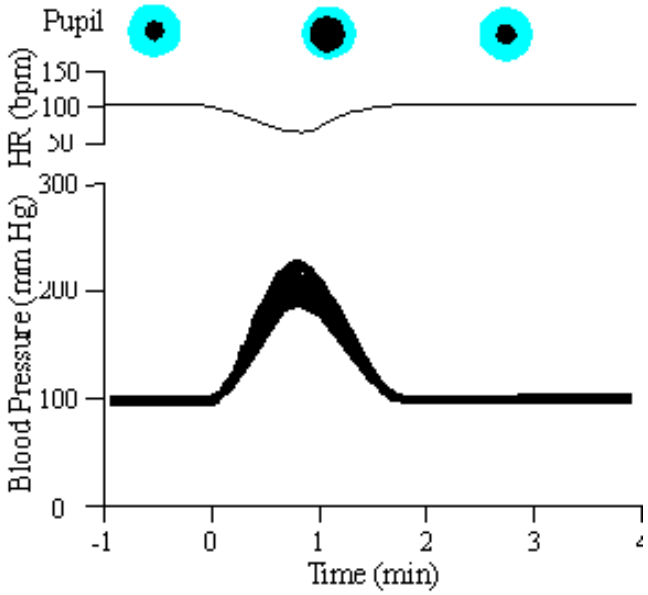
Foils "a", "b" and "c" are correct: Although the action of neuronally-released norepinephrine is terminated primarily by reuptake, COMT and MAO metabolism plays an important role in terminating the action of exogenously administered epinephrine and norepinephrine. Esterases play a role in termination of action of acetylcholine

4. Recall in the graph of epinephrine administration, after the increase in blood pressure, the pressure made a slight dip below the base line before returning to normal. What is (are) the most likely explanation(s) for this?
   a. The BP falls so fast that this is a normal rebound phenomenon.
   b. This is a result of β-2 receptor stimulation.
   c. The α receptors become tolerant to continued stimulation.
   d. This results from the "low dose" effect of epinephrine.

Foils "b, d" are correct: Epinephrine -at low dose- stimulates the β-$_2$ receptor resulting in vasodilation and decrease of the arterial blood pressure. This may appear at the end of the pressure tracing when the effect of α receptors disappears.

That's enough for epinephrine. The blood pressure should be back to normal now, so let's try norepinephrine. The dose will be 1 μg (base)/kg. The action of norepinephrine is quickly terminated in a manner similar to that of epinephrine.

This is the effect of norepinephrine 1µg /kg



5. The rise in blood pressure produced by norepinephrine results from:
   a. Increased cardiac output
   b. Increased total peripheral resistance.
   c. β receptors stimulation.
   d. α receptors stimulation.

The second and fourth foils are correct: The rise in blood pressure is primarily due α-1 receptor stimulation resulting in vasoconstriction and increased total peripheral resistance. Think of how the responses would be modulated by reflex activity. The cardiac output decreased due to reflex bradycardia as well as vasoconstriction.

6. Hopefully, you noticed that norepinephrine produced a decrease in heart rate. The decrease in heart rate resulted from:
   a. A direct β-stimulant effect on the heart.
   b. Increased baroreceptors activity.
   c. A direct α-stimulant effect on the heart.
   d. Reflex activation of the parasympathetic system secondary to the rise of blood pressure induced by norepinephrine.

The second and fourth foils are correct: Norepinephrine – unlike epinephrine- leads to marked rise in BP due to unopposed

α-action. This triggers the parasympathetic (vagal) reflexes.

7. If the animal had been previously vagotomized, norepinephrine would have produced an increase in heart rate instead of a decrease. Such an effect would be a manifestation of:
    a. α receptors stimulation induced by norepinephrine.
    b. A reflex increase in sympathetic activity.
    c. β-$_2$ receptors stimulation induced by norepinephrine.
    d. β-$_1$ receptors stimulation induced by norepinephrine.

Only foil "d" is correct: The heart contains both β-1 (80%) and β-$_2$ (20%); however, norepinephrine stimulates only β-$_1$ adrenoceptors.

8. A sufficiently small dose of epinephrine will produce a decrease in mean BP. What will happen with administration of a comparably small dose of norepinephrine?
    a. There will be a decrease in mean BP similar to epinephrine.
    b. The mean BP would probably increase.
    c. There will be a greater decrease in mean BP than with epinephrine.
    d. The dose will primarily stimulate β-$_2$ receptors.

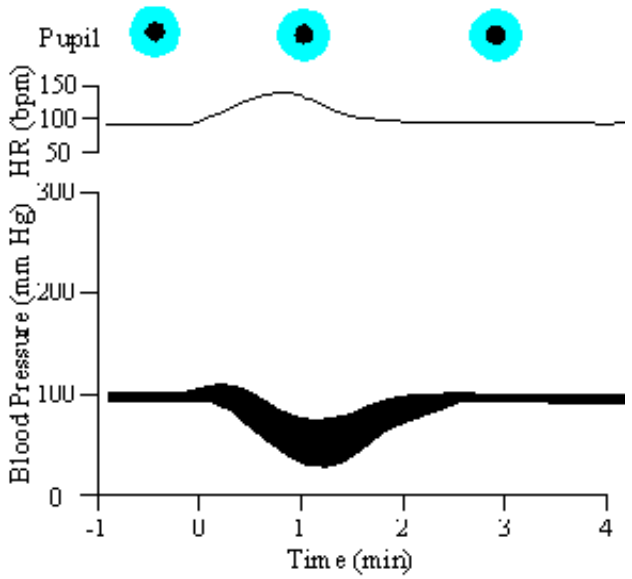
The correct answer is b.
There is no "low dose" effect with norepinephrine. That dip which you saw in the graph of epinephrine is a result of the "low dose" effect of epinephrine. That is, because the blood concentration of epinephrine is being reduced by reuptake and metabolism, the concentration the receptors are exposed to becomes so small that we see a predominant β-$_2$ effect on the blood pressure. We do not see this with norepinephrine because the drug has little or no effect on β -$_2$ receptors.

The next drug will be isoproterenol HCI in a dose of 1 µg /kg.

9. What would you expect the mean BP to be after administration of isoproterenol?
   a. The same or slightly higher
   b. lower
   c. Unchanged
   d. Much higher
   e. None of the above

The answer is b. Cardiac output is increased due to the positive inotropic and chronotropic effects of the drug. An increased cardiac output is generally able to cause an increased systolic pressure. However, there is a very strong effect of β -2 receptor activation. The β -$_2$ effect of the drug causes a marked decrease in the diastolic blood pressure blood pressure and the net effect is a fall in the mean blood pressure.

Effect of isoproterenol HCI in a dose of 1 µg /kg



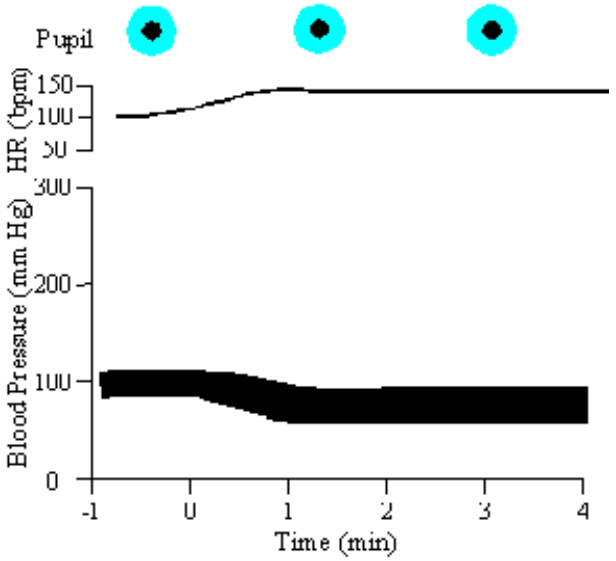
10. Other actions of isoproterenol include:
    a. Bronchodilation.
    b. Decreased uterine tone.
    c. Decreased GI motility.
    d. Increase in plasma free fatty acids.

All foils are correct.

We now proceed to the administration of our next drug, phentolamine HCI, the dose to be administered is 2 mg/kg.

11. Which of the following is true about phentolamine?
    a. Phentolamine is a competitive α receptor blocker.
    b. Phentolamine exerts a 'sympatholytic' effect in the heart.
    c. The mean BP increased after phentolamine administration.
    d. The pupil diameter will increase with phentolamine.
    e. All of the above.

Only foil "a" is correct. Phentolamine exerts a hypotensive effect through its sympatholytic action on the blood vessels (which contain α receptors) but not on the heart (which contains β receptors). The pupil diameter may decrease if the sympathetic supply to the dilator pupillae muscle is already stimulated before.

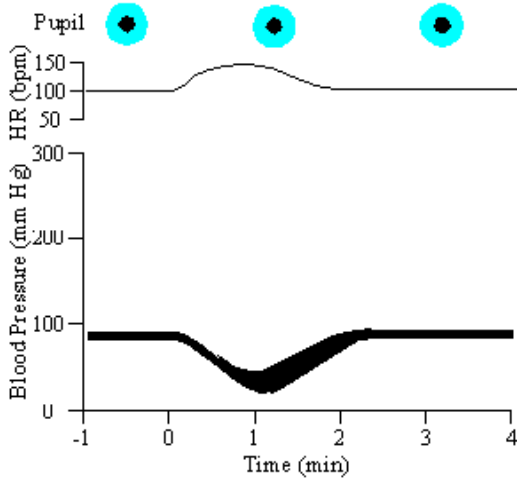


12. The widening pulse pressure accompanied by a decreased mean blood pressure can be attributed in part to:
    a. Vasodilation due to α-$_1$ receptor blockade.
    b. Increased parasympathetic discharge.
    c. Decreased myocardial contractility.
    d. Decreased HR.
    e. All of the above.

Only foil "a" is correct. Phentolamine-induced hypotension leads to cardiac stimulation due to reflex sympathetic activation.

13. After administration of an α blocker, what would you expect the mean blood pressure to be on subsequent administration of epinephrine?
    a. The BP would decrease due to stimulation of β-$_2$ receptors in the blood vessels.
    b. The BP would stay the same due to α receptor blockade.
    c. The BP would increase due to β-$_2$ receptor stimulation.
    d. The BP would increase due to α receptor blockade.
    e. The BP would decrease due to stimulation of β-$_1$ receptors in the heart.

Only foil "a" is correct: after α receptors blockade, epinephrine acts the same as isoproterenol (isoprenaline). The phenomenon where the blood pressure decreases with a "high" dose of epinephrine, after administration of an α blocker, is known as "epinephrine reversal".



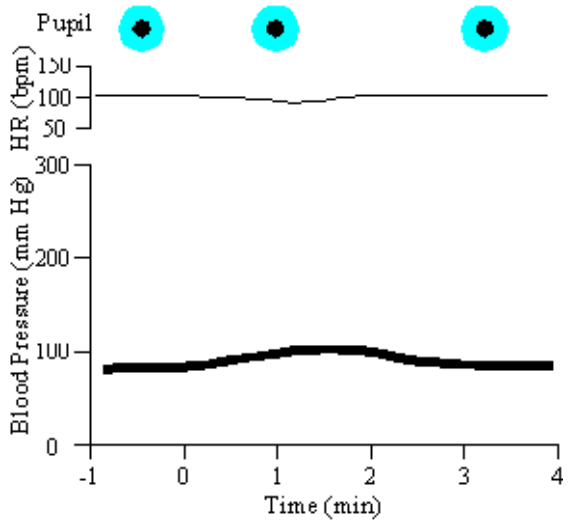
14. There is no mydriasis in this case because:
    a. β receptors are stimulated.
    b. β receptors are blocked.
    c. β receptors are not stimulated.
    d. α receptors are stimulated.
    e. α receptors are blocked.

Only Foil "e" is correct: The dilator pupillae muscle contains α receptors only.

15. In the previous BP tracing, the HR increased when the blood pressure dropped. This resulted from:
    a. Reflex decrease in parasympathetic tone.
    b. Reflex increase in sympathetic tone.
    c. β receptor activation.
    d. A direct effect of epinephrine on the heart.

All foils are correct: In addition to the direct cardiac β-$_1$ stimulatory effect of epinephrine, the hypotensive effect after phentolamine leads to activation of the sympathetic and inhibition of the parasympathetic reflexes on the heart.

Norepinephrine at a dose of 1 µg (base)/kg is now given



Notice that the administration of phentolamine has markedly reduced the rise in blood pressure produced by norepinephrine. This of course, is related to the fact that the vasoconstrictor action of norepinephrine is antagonized by phentolamine. However, phentolamine did not reverse the pressor response to norepinephrine, as was the case with epinephrine.

16. What is the best explanation for this different effect of norepinephrine when compared to epinephrine?
    a. Norepinephrine has a much greater stimulant action than epinephrine at α-$_1$ receptors.

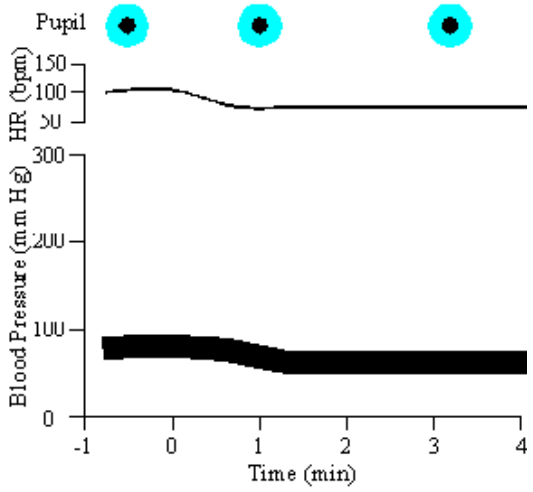
b. Norepinephrine has little or no agonistic action at β-1 receptors.
c. Norepinephrine is a potent β_2 receptor agonist
d. Norepinephrine has little or no stimulant action at β_2 receptors.
e. Norepinephrine is a potent β_1 stimulant

Only foil "d" is correct: After α receptors blockade, norepinephrine acts on cardiac β_1 receptors leading to slight increase in BP.

The next drug to be given is isoproterenol HCI at 1 µg /kg.

17. What would you expect its effect on mean blood pressure to be now that phentolamine has been administered?
    a. BP will decrease the same as it did before phentolamine.
    b. BP will increase due to increased cardiac output
    c. BP will decrease more markedly than before phentolamine.
    d. BP will decrease due to decreased HR.
    e. All of the above are possible.

The answer is c. Think about what actions are blocked. The hypotensive effect of phentolamine is summated to that of isoprenaline. This is what happens when we give isoproterenol after phentolamine.



18. Why the action of isoproterenol prolonged as compared to its effects before phentolamine?
    a. The β_2 receptors are now more sensitive to the drug.

b. The α receptors are no longer responsive to sympathetic reflexes.
c. The β-$_1$ receptor-mediated response is blocked.
d. The β-$_2$ receptors are blocked.
e. None of the above.

The answer is b. The counter regulatory reflex sympathetic stimulation (which is triggered by the hypotensive effect of isoproterenol) does not work because the α receptors are already blocked.

The next drug will be propranolol HCI a dose of 0.5 mg/kq.
It must be given very slowly; otherwise our cat might not survive. While we are waiting for the remainder of the propranolol to be administered, let me remind you that the main point of this lab (which we hope is clear to you) – is that the agonists and antagonists we are giving are relatively selective for specific receptors at THERAPEUTIC doses.

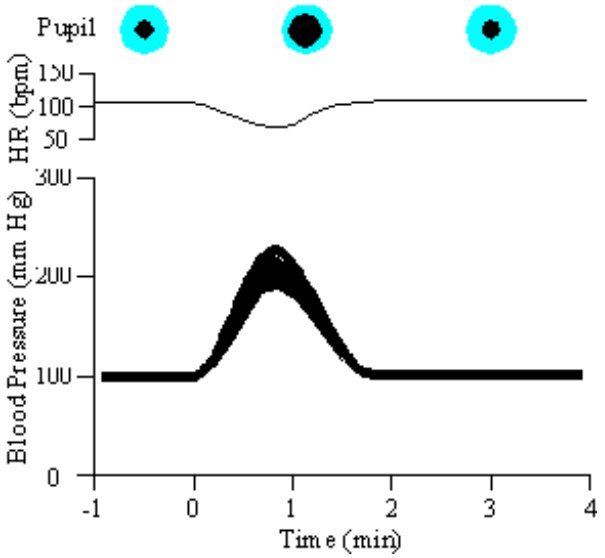
19. After administration of phentolamine and propranolol to this cat, we have effectively blocked the:
    a. α-$_1$ receptors.
    b. β-$_1$ receptors.
    c. α-$_2$ receptors.
    d. β-$_2$ receptors.

All foils are correct.

20. If we re-administer isoproterenol HCI 1 μ/kg, what would you expect the response to be?
    a. No change in systolic BP.
    b. No change in HR.
    c. No change in diastolic BP.
    d. No change in mean BP.

All foils are correct.
The cat we have been working with has been treated with both phentolamine and propranolol. Although these are both competitive inhibitors, it would take at least several hours for their effects to wear off completely such that they would not interfere with the effects of a few additional adrenergic agents we need to look at.
Thus, we will start a new series of experiments using a fresh cat which has been prepared as described earlier and has not been treated with any adrenergic agonists or antagonists.

The first drug we want to try is norepinephrine 1 µg (base)/kg.



The next drug we want to administer is tyramine 10 µg/kq.

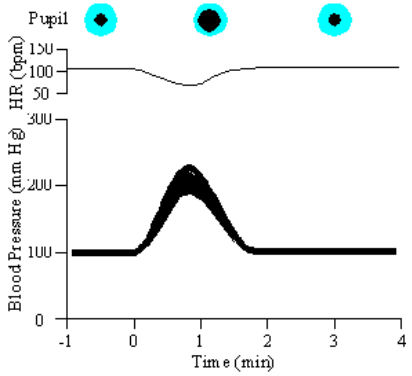
21. Tyramine acts by:
    a. Inhibiting α receptors.
    b. Directly stimulating β receptors.
    c. Directly stimulating α receptors.
    d. Stimulating release of norepinephrine.
    e. inhibiting release of norepinephrine

Only foil "d" is correct. Tyramine –like ephedrine and amphetamine- is an indirectly acting sympathomimetic agent.

22. Which of the following do you predict? Tyramine will:
    a. Not change in BP or HR.
    b. Decrease BP and HR.
    c. Increase BP and HR.
    d. Decrease BP and increase HR.
    e. Increase BP and decrease HR

The answer is e. Think of what norepinephrine does. The rise in blood pressure is primarily due to norepinephrine released from adrenergic neurons. Remember, HR decreases in response to norepinephrine as a result of the baroreceptors reflex.

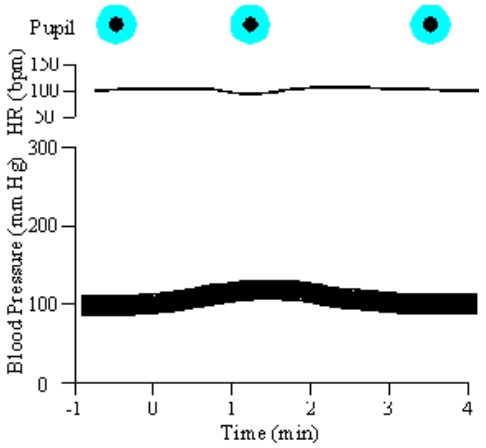
This figure shows the effects of tyramine 10 µg (base)/kg.
(The responses look similar to those induced by norepinephrine.)



23. Repeated administration of the same dose of tyramine several times, which of the following would you expect?
    a. No change in the response.
    b. A markedly exaggerated response.
    c. A markedly depressed response.
    d. A reversed response.

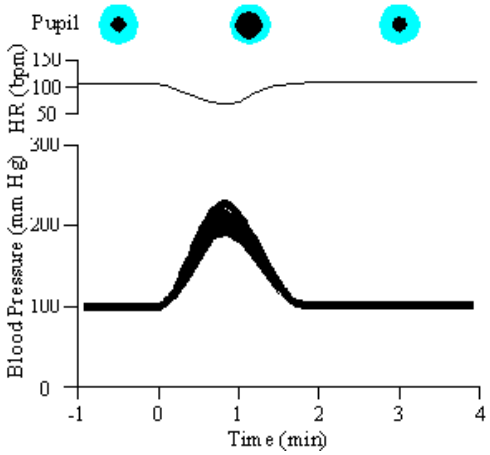
The answer is c. A limited pool of norepinephrine is available for release by tyramine resulting in the rapid development of tolerance or tachyphylaxis. Let's try tyramine again and see.

This figure shows the effect of tyramine 10 µg/kg.



Notice that the rise in blood pressure and decrease in heart rate are markedly reduced when compared to what we saw before.
To rule out desensitization at, or subsequent to, the receptor level, let's see if the response to norepinephrine has changed.

This figure shows the effects of norepinephrine 1 μg (base)/kg.
(The response looks pretty much the same as it did before.)



24. Which of the following would inhibit responses to tyramine, but tend to enhance responses to norepinephrine?
    a. Inhibition of α receptors.
    b. Inhibition of β receptors.
    c. Inhibition of both α and β receptors.
    d. Inhibition of neuronal reuptake.

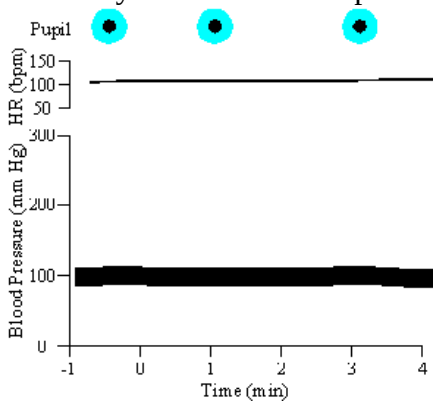
Only foil "d" is correct: The effect of norepinephrine is enhanced since its termination of action by reuptake is inhibited.

25. Which of the following would be a good drug for us to use as a reuptake inhibitor in our experiments?
    a. Phenylephrine
    b. Imipramine
    c. Prazosin
    d. Amphetamine
    e. Pargyline

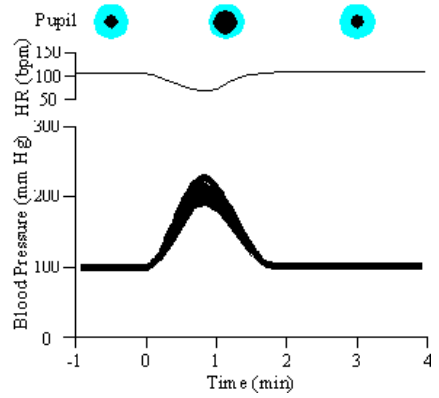
Only foil "b" is correct: Imipramine is a TCA that inhibits the reuptake pump of monoamines. Phenylephrine is a selective α-$_1$ agonist while prazosin is a selective α-$_1$ blocker. Amphetamine is an indirectly acting sympathomimetic that releases as well as inhibits the reuptake of norepinephrine. Pargyline is a MAOI.

By now, we have waited long enough for the response to tyramine to return to control levels (particularly since we have also administered norepinephrine which would also tend to reload depleted neuronal pools).
Let's see what the administration of imipramine 2.5 mg/kg does to subsequent responses to tyramine and norepinephrine.

This is the effect of tyramine 10 µg/kg after imipramine. Imipramine essentially abolished the response to tyramine.



Let's see what imipramine does to norepinephrine-induced responses. This is the effect of norepinephrine 1 µg (base)/kg after imipramine



The response looks relatively unchanged. Although you might have expected more dramatic potentiation of norepinephrine in the presence of an uptake inhibitor, this is largely balanced by a simultaneous action of imipramine to inhibit alpha adrenergic receptors.

26. Pretreatment with which of the following would you expect to also inhibit responses to tyramine, but not responses to norepinephrine?
    a. Phenoxybenzamine
    b. Tranylcypromine
    c. Cocaine
    d. Iproniazid
    e. Yohimbine

Only foil "c" is correct: Cocaine inhibits the neuronal reuptake of norepinephrine as well as of tyramine. Phenoxybenzamine is a selective α-$_1$ blocker while yohimbine is a selective α-$_2$ blocker. Tranylcypromine & iproniazid are MAOIs.

27. Effects of reserpine include:
    a. Inhibition of dopamine uptake into vesicles within adrenergic nerve endings.
    b. Inhibition of norepinephrine synthesis.
    c. Depletion of norepinephrine from adrenergic nerve endings.
    d. Inhibition of norepinephrine reuptake at the neuronal membrane.

The first and third foils are correct.
Except at extremely high concentrations attainable in vitro, reserpine does not inhibit the amine pump which transports norepinephrine and other amines across the neuronal membrane.

II. CHOLINERGIC AGONISTS AND ANTAGONISTS

It would be very helpful if you review your lecture notes and/or your text concerning the subject material to be covered in this lab experiment. The purpose of this lab is to demonstrate some of the effects of drugs which influence the parasympathetic nervous system and its effector organs.

In the last experiment, we anesthetized a cat and prepared it for recording blood pressure, heart rate. Well, use the same system here too. We were lucky to obtain a cat which again weighs exactly 2 kg. It was anesthetized with pentobarbital 35 mg/kg. This cat should be adequately anesthetized for about 6 hours. We cannulated the animal as we did in the first experiment so you should have no problems proceeding with the experiment.

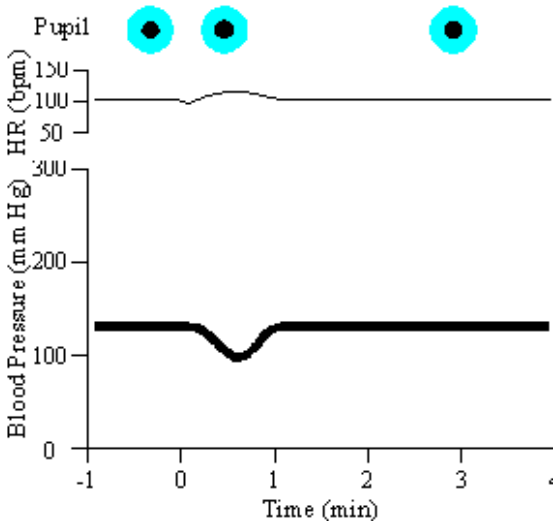
1. Which of the following is true about acetylcholine (Ach)?
   a. It stimulates the muscarinic receptors
   b. It stimulates the adrenal medulla
   c. It is released from parasympathetic pre- and postganglionic nerve endings
   d. It is a mediator at both sympathetic and parasympathetic ganglia

All foils are correct: Ach is released from all preganglionic nerves (sympathetic and parasympathetic), from all post ganglionic parasympathetic as well as from some post ganglionic sympathetic nerves (sympathetic cholinergic fibers). Ach is also released from the motor nerves to the skeletal muscles and from some nerve fibers in the CNS.

2. Ach would directly produce which of the following?
   a. Miosis
   b. Increased GI motility
   c. Bronchoconstriction
   d. Glycogenolysis

The first 3 foils are correct: Remember, Ach is <u>secretory</u> (to exocrine glands) <u>motor</u> (to smooth muscles). Glycogenolysis is mediated in human by β-2 adrenoceptors (85%) and α-1 adrenoceptors (15%).

Finally, we are ready to see what happens with 0.1 µ/kg of Ach.



Effect of 0.1 µ /kg Ach

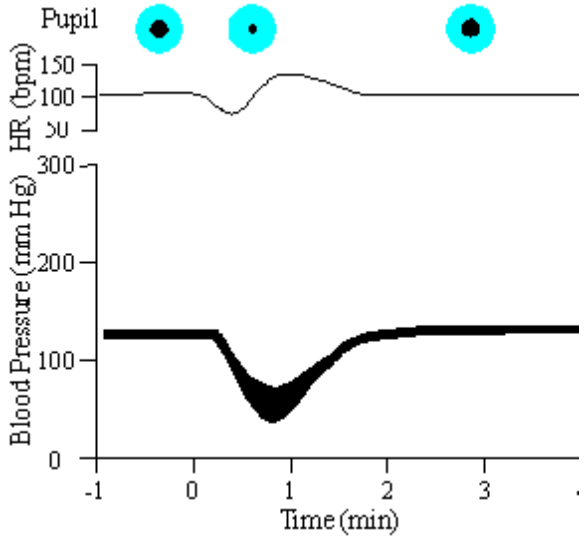
3. Why would there be minimal effects on the cardiovascular system with this dose of Ach?
    a. Rapid destruction of the compound
    b. Cardiovascular compensatory reflexes
    c. The dose is small
    d. Tolerance to Ach

Foils "a, b,c" are correct: The small dose of Ach stimulates endothelial M_3 receptors to release NO with subsequent vasodilatation and decrease of BP. The lack of effect on HR may be due to either rapid hydrolysis of the small dose of Ach before it reaches the heart or because Ach-induced bradycardia was counteracted by reflex sympathetic stimulation 2^{ry} to decreased BP.

4. Which enzyme(s) is/are responsible for the rapid termination of the actions of Ach?
    a. Acetylcholine esterase
    b. MAO
    c. Anticholine esterase
    d. Pseudo-choline esterase
    e. Methyl choline esterase

Foils "a" and "d" are correct: Exogenous Ach is hydrolyzed both by plasma pseudo choline esterase as well as by nervous true Ach esterases.

What happens when we increase the dose of Ach to 0.5 µg/kg?



Effect of 0.5 µ/kg of Ach

5. The increase in the heart rate seen after the administration of the drug is due to
    a. Direct action of the drug on the heart
    b. Sympathetic reflex stimulation
    c. Complete metabolism of the drug by Ach esterase
    d. Vasoconstriction of the splanchnic vessels
    e. None of the above

Foils "b and c" are correct. Remember what happens to the blood pressure with Ach:

The HR and BP initially decrease due to a direct action of the drug on the muscarinic receptors of the heart and the endothelium lining the blood vessels. Because of reflex mechanisms, there is an increased sympathetic discharge producing an increase in the heart rate and returning the peripheral resistance toward normal. This, along with rapid destruction of Ach by cholinesterase restored the mean blood pressure. We must also remember that still larger doses of Ach also stimulate nicotinic receptors and cause the release of epinephrine and norepinephrine from both the adrenal medulla and the sympathetic postganglionic nerves.

The next drug will be neostigmine methyl sulfate (0.05 mg/kg):

6. Which of the following is a property of neostigmine?
    a. It is an anticholinesterase
    b. It blocks muscarinic receptors
    c. It acts on skeletal muscle
    d. It irreversibly binds to cholinesterase

Foils "a" and "c" are correct: neostigmine is a reversible anticholine esterase; leading to preservation of Ach with subsequent stimulation of both muscarinic and nicotinic receptors. In addition, neostigmine can stimulate the skeletal muscle nicotinic receptors (Nm receptors) by itself.

7. Now that we know that neostigmine is an anticholinesterase, let's discuss what happens at some of the organs affected by this drug. When neostigmine is applied locally to the eye, which of the following changes can take place
    a. Miosis
    b. Decreased intraocular pressure
    c. Spasm of accommodation
    d. Constriction of the intraocular vessels

The first 3 foils are correct: Neostigmine indirectly stimulates M_3 receptors through preservation of Ach. This results in contraction of the constrictor pupillae muscle (miosis) and ciliary muscle (accommodation) with subsequent opening of the canal of Schlem (decrease intraocular pressure). On the contrary, Ach dilates the intraocular blood vessels (leading to red eye).

8. If neostigmine prolongs the action of endogenous Ach, what would we expect neostigmine's effect on the BP to be?
    a. No change because there is little cholinergic innervation in the blood vessels
    b. The BP would markedly decrease due to enhanced effects of endogenous Ach
    c. The BP would markedly decrease because of the decreased HR
    d. The BP would increase because of sympathetic stimulation
    e. All of the above could occur

Foil "a" is correct.

We won't show you on a graph what happens to the blood pressure tracing after the administration of neostigmine because nothing usually happens except some miosis, but just remember that we gave neostigmine and its effects will last for the duration of the experiment

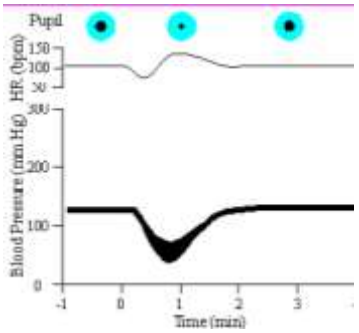
Now if we give the same dose of Ach (0.1 µ/kg) after neostigmine

9. What will happen now if we give a small dose of Ach (0.1 µ/kg)?
    a. The BP will show the same effect as before the administration of neostigmine
    b. The response will be similar to a large dose of Ach
    c. The BP will remain the same
    d. There will be a prolonged increase in the BP
    e. There will be a decrease in the BP but less than before neostigmine

Only foil "b" is correct.

If we give 0.1 µ/kg of Ach after neostigmine, this is what happens:

It produces the same action as a large dose.



10. What would happen if we administered Ach in a large dose (0.5 µg/kg) after neostigmine?
    a. There would be a parasympathomimetic effect
    b. There would be no change in the BP
    c. There would be a prolonged effect
    d. The BP would show a biphasic response characteristic of large doses of Ach

The correct answer is C: If a large dose of Ach is given after neostigmine you would still get the same response except that the magnitude and duration of the response would be greater since Ach is not metabolized.

The next drug to be administered will be atropine sulfate 1 µg/kg:

11. What would you expect the effects to be?
    a. Bronchoconstriction
    b. Increase in the heart rate
    c. Urinary incontinence
    d. Miosis

Only foil "b" is correct: Atropine is a competitive muscarinic blocker.

12. The following can be attributed to atropine administration:
    a. Constipation
    b. Mydriasis
    c. Dry mouth
    d. Increased urination

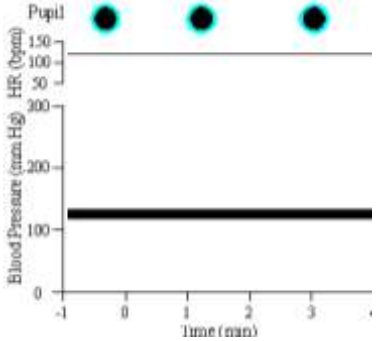
Foils "a", "b" and "c" are correct: Atropine relaxes the smooth muscles and dries the exocrine secretions.

Since nothing of any significance happens to the BP after the administration of atropine, let's proceed to the next drug.

Ach will be given in a dose of 0.5 µ /kg:

13. After administration of this dose (0.5 µg/kg) of Ach, which of the following would be true?
    a. The muscarinic receptors are blocked so there will be an initial fall in the BP
    b. There will be a decrease in the mean BP
    c. There will be an increase in the mean BP
    d. There will be no change in the mean BP

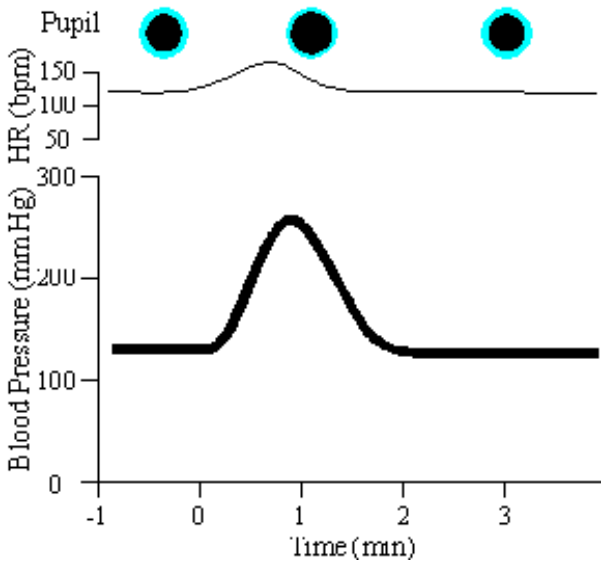
Foil "d" only is correct: Ach induces no change in BP since the muscarinic receptors were already blocked by atropine and the dose was too small to stimulate the nicotinic receptors. Let's refer to our pressure tracing to confirm what is happening:



Now we gave Ach in a dose of 0.5 mg/kg:

14. What would you expect with this extremely large dose (Note that this dose is 1000 X larger than our previous dose of o.5 µg/kg):
    a. The BP would increase
    b. The BP would decrease then increase in a biphasic response
    c. The BP would decrease
    d. The BP would not significantly change
    e. None of the above

Only foil "a" is correct: This is what happens with very large dose of Ach.



15. Why, when we administered a dose of Ach which is extremely large, did we get an increase in BP?
    a. The vessels do not have any cholinergic receptors
    b. The muscarinic effect of Ach is effectively blocked by atropine so nicotinic effects become apparent
    c. This dose blocks the adrenergic receptors
    d. This dose stimulates the adrenergic receptors
    e. None of the above

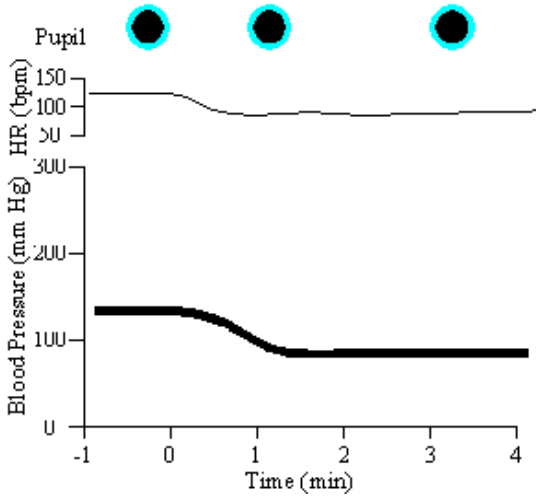
Only foil "b" is correct: This is due to stimulation of the nicotinic receptors of the adrenal gland and sympathetic ganglia with subsequent release of epinephrine and norepinephrine.

Hexamethonium is the next drug which our animal will receive:

16. Do you remember what the actions of hexamethonium are? Let's see what you can recall. Hexamethonium has the following action(s)
    a. It antagonizes the effects of nicotine
    b. It antagonizes the effects of DMPP
    c. It is a ganglionic blocker
    d. It inhibits the muscarinic receptors

The first three foils are correct: Hexamethonium is a ganglion blocker; so it antagonizes the effects of ganglion stimulants as nicotine. You may not have heard of DMPP: it is short for dimethylphenylpiperazinium. (Now you know why most people called DMPP). Anyway, DMPP is a ganglionic stimulant which acts in a manner similar to nicotine.

Getting back to the ganglionic blocker, hexamethonium let's see what happens when we administer a dose of 2 mg/Kg:



17. Why did hexamethonium decrease the HR?
    a. Hexamethonium blocks beta receptors
    b. Hexamethonium stimulates muscarinic receptors
    c. Hexamethonium blocks sympathetic ganglia
    d. Vagal stimulation
    e. None of the above

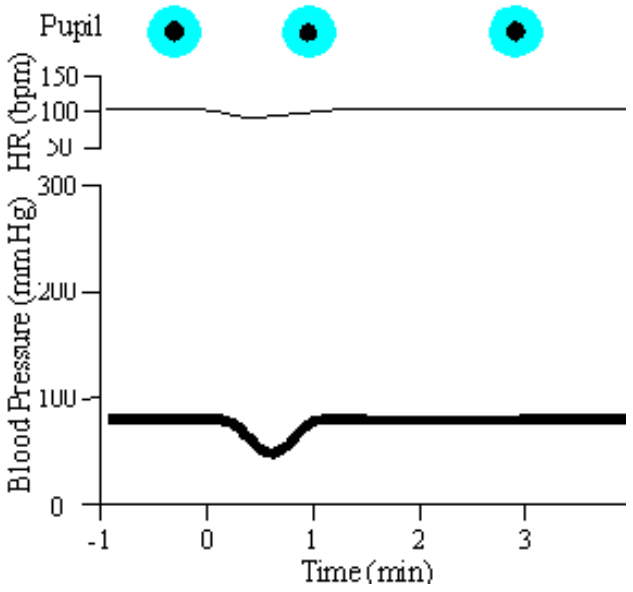
Only foil "c" is correct: Although hexamethonium blocks both types of the autonomic ganglia; the effect of the sympathetic ganglia is dominant on BP.

We are now ready to administer a super large dose of Ach (0.5 mg/kg) once again:

18. Administration of Ach will now produce which of the following?
    a. No change in the mean BP
    b. No change in the systolic BP
    c. No change in the heart rate
    d. Decreased BP

Only the fourth foil is correct: Hexamethonium has blocked the nicotinic actions of the super large dose of Ach. The latter now produces a small fall in blood pressure as a manifestation of a residual effect on muscarinic receptors (which were incompletely blocked by the dose of atropine employed).

Let's confirm our prediction, that a large dose of Ach in the presence of atropine and hexamethonium will cause a fall in blood pressure.



III. UNKNOWN AUTONOMIC DRUGS

This lab is designed to test what you have learned in the adrenergic and cholinergic labs. We have a series of unknown pharmacological agents which you will try to identify using the knowledge developed in the first two lab sessions. Please do not attempt this lab exercise until you have completed the previous 2 labs. Although you don't need to know it for examinations, we remind you that DMPP is a selective agonist at nicotinic receptors in ganglia and will be used as a pharmacological tool in this exercise. This lab should be an interesting one because it tests how you apply your skills on pharmacological knowledge.

We were able to obtain a number of cats to work with, so we will be able to test whether you can identify unknown drugs. All of these animals have been anesthetized and prepared as described previously. Possible unknowns and the drugs for your use in trying to identify the unknowns are:

epinephrine DMPP propranolol isoproterenol

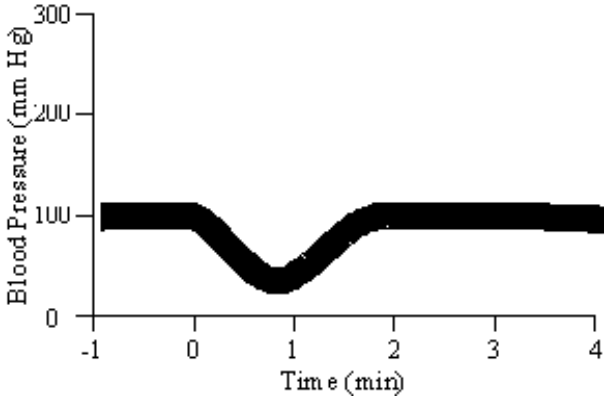
tyramine Ach atropine neostigmine hexamethonium
imipramine norepinephrine phentolamine

Each of these drugs may be used once, more than once, or not at all.

You don't have to worry about the dose that is administered, because each of the drugs is made up in a concentration sufficient to exert an effect when the drug is injected.

Before starting, let's give you a few helpful hints. By systematically choosing the known drugs, you should be able to deduce what the unknown is. On the basis of the mean blood pressure tracings, as well as a few hints which we will occasionally give to you, there should be no difficulty in identifying the unknown drugs. Please note that unlike the first two labs, the BP tracings show mean pressure only. Occasionally, we may give you some hints as to a reasonable order of drug administration. It is up to you to get the right answer by using the available knowns.

Unknown Agonist 1:



1. Choose all of the following drugs would you consider as possibilities for the identity of the unknown?
    a. Epinephrine
    b. DMPP
    c. Isoproterenol
    d. Ach
    e. Norepinephrine
    f. Tyramine

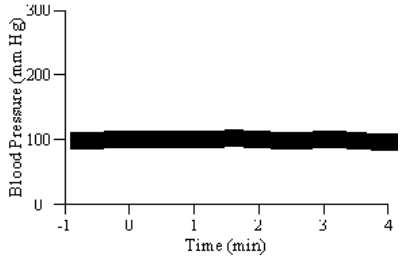
Foils "a", "c" and "d" are correct: Epinephrine and isoproterenol (through β-2 mediated vasodilation) and Ach (through M-mediated vasodilation and bradycardia) can decrease BP.

2. Knowing that the possible agonists are epinephrine, isoproterenol and Ach, choose all of the following which would be logical antagonists to administer in an attempt to identify this unknown?
    a. Atropine
    b. Phentolamine
    c. Propranolol
    d. Hexamethonium

Foils "a" and "c" are correct: Propranolol to block β-2 receptors and atropine to block M receptors

We will give atropine first

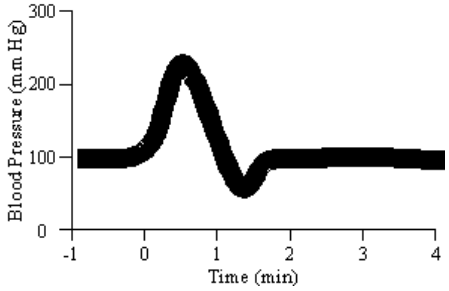
Okay, this is the response to the unknown after the cat was given atropine:



3. What do you think the unknown is?
    a. Epinephrine
    b. DMPP
    c. Isoproterenol
    d. Ach
    e. Norepinephrine
    f. Tyramine

Foil "d" is correct: since the action is blocked by atropine.

Unknown agonist 2:



4. Choose all of the following drugs which you consider as possible candidates for the unknown?
    a. Epinephrine
    b. DMPP
    c. Isoproterenol
    d. Ach
    e. Norepinephrine

Foils "a", "b" and "e" are correct: Epinephrine and norepinephrine (through α-mediated vasoconstriction) and

DMPP (through N-mediated sympathetic ganglion stimulation) can increase BP. The late decrease in BP may be attributed to β-2 mediated vasodilation (epinephrine), N-mediated parasympathetic ganglion stimulation (DMPP) or reflex bradycardia persisting after termination of the pressor action (norepinephrine).

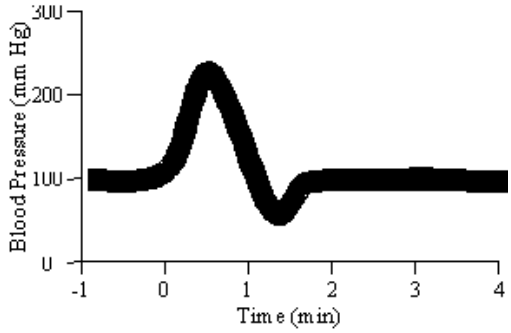
5. Knowing the possible agonists, (see previous question), choose all of the following which you would administer as possible antagonists?
    a. atropine
    b. phentolamine
    c. propranolol
    d. hexamethonium

Foils "b" and "d" are correct: Phentolamine to block α receptors or hexamethonium to block N receptors.

6. Which of the antagonists would you like to administer first phentolamine or hexamethonium? Note that the sequence of administration is important here so think about this carefully.
    a. Phentolamine
    b. Hexamethonium

If the unknown were DMPP or norepinephrine, you would not be able to distinguish between them if you gave the alpha blocker first because it would block both agonists. It would be wise to give hexamethonium first, and then you could distinguish between them.

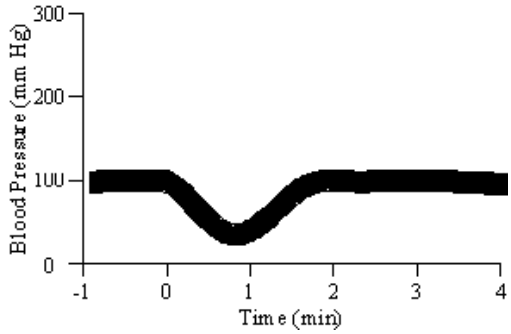
Here is what we get with our unknown after hexamethonium.



Since this did not block the effect, hence DMPP is excluded.

Now we can give the α blocker, phentolamine.

After pretreatment with phentolamine, the unknown produced the following:

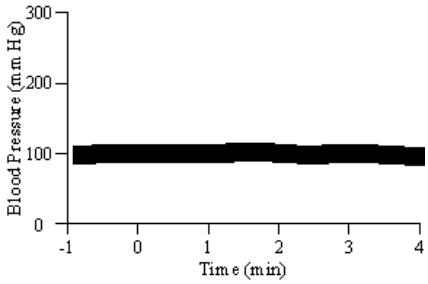


Since phentolamine REVERSED the original pressor response to a depressor response; norepinephrine can be excluded.

7. Which of the following would you like to administer now to confirm:
    a. Atropine
    b. Phentolamine
    c. Propranolol
    d. Hexamethonium
    e. Neostigmine

Foils "c" is correct: propranolol can be used to block the β-2 receptors

The effect of an unknown in our cat pretreated with propranolol.

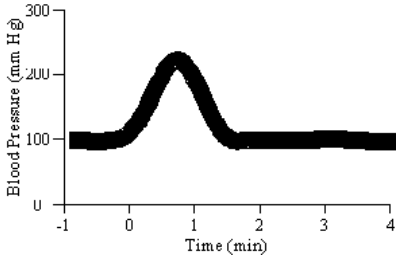


(Don't forget this cat has also received hexamethonium and phentolamine)

8. So what is the unknown agonist?
    a. Epinephrine
    b. DMPP
    c. Isoproterenol
    d. Ach
    e. Norepinephrine

Since phentolamine reversed the pressor response, and propranolol blocked the depressor response, the unknown must be epinephrine.

Unknown agonist 3:

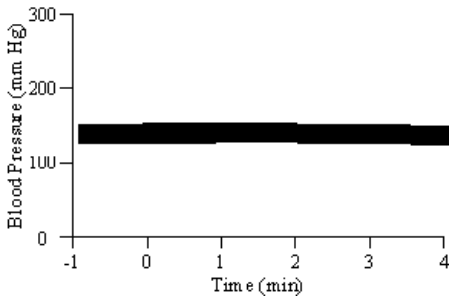


9. Which antagonist would you like to inject first into this animal?
    a. Atropine
    b. Phentolamine
    c. Propranolol
    d. Hexamethonium

The answer is D, hexamethonium. The unknown increased BP so the antagonists are phentolamine and hexamethonium but

we must give the ganglionic blocker before the α blocker to distinguish between a ganglionic stimulant and an α agonist.

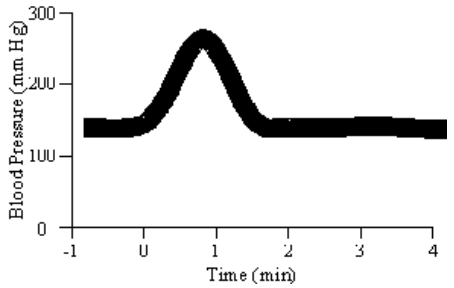
After hexamethonium the unknown produced a GREATER increase in BP (tracing not shown). This tracing is the response to the unknown agonist after the cat was administered phentolamine.



10. What do you think the unknown is?
    a. Epinephrine
    b. DMPP
    c. Isoproterenol
    d. Ach
    e. Norepinephrine

Foil "e" is correct: An α blocker blocked the pressor effect of the unknown, and there was no epinephrine reversal.

Unknown agonist 4:

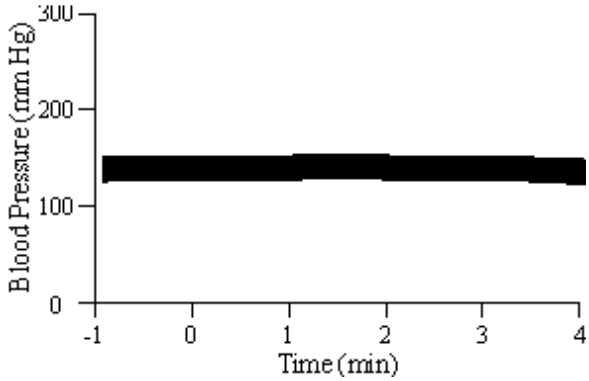


11. Which antagonist would you like to inject into the animal first?
    a. Atropine
    b. Phentolamine
    c. Propranolol

d. Hexamethonium

Foil "d" is correct.

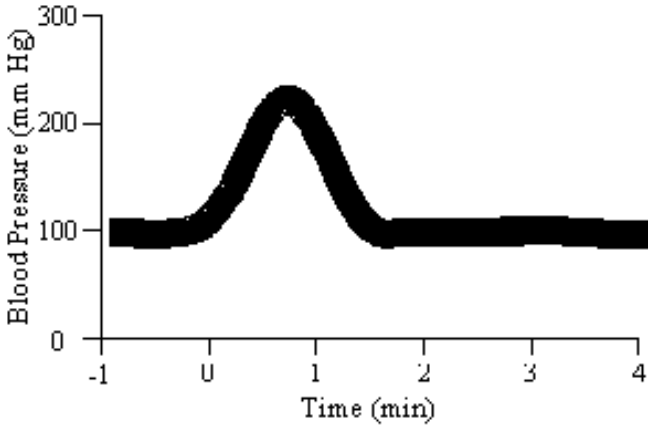
Either hexamethonium alone OR phentolamine alone would have blocked the response to the unknown agonist.



12. What is unknown agonist 4?
    a. Epinephrine
    b. DMPP
    c. Isoproterenol
    d. Ach
    e. Norepinephrine

Foil "b" is correct.

Unknown agonist 5:



13. Which of the following agonists could be the unknown?
    a. Epinephrine
    b. DMPP
    c. Isoproterenol
    d. Ach
    e. Norepinephrine
    f. Tyramine

All foils but "c" and "d" are correct: Epinephrine and norepinephrine (through α-mediated vasoconstriction), DMPP (through N-mediated sympathetic ganglion stimulation) or tyramine (through stimulating norepinephrine release) can increase BP.

14. Which antagonist would you like to inject first into this animal?
    a. Atropine
    b. Phentolamine
    c. Propranolol
    d. Hexamethonium
    e. Imipramine

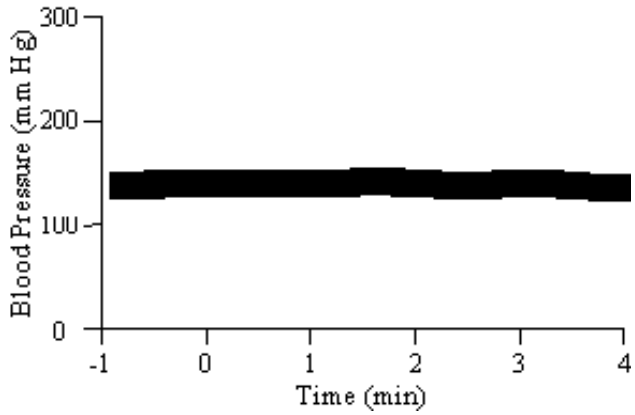
Foil "d" is correct.

After hexamethonium the unknown produced a GREATER increase in BP (tracing not shown).

15. Which of the following would you like to administer next?
    a. Atropine
    b. Phentolamine
    c. Propranolol
    d. Imipramine

The best choice is d, imipramine. If you give phentolamine now, you won't be able to distinguish norepinephrine from tyramine.

The following tracing is the response to the unknown agonist after the cat was administered imipramine.



16. Which do you think the unknown is?
    a. Epinephrine
    b. DMPP
    c. Isoproterenol
    d. Ach
    e. Norepinephrine
    f. Tyramine

The answer foil "f"; tyramine. The neuronal uptake inhibitor imipramine completely blocked the pressor effect of the unknown.

How to Write a Prescription

- **Drug:** chemical substance
  - used for **treatment**, **diagnosis** or **prophylaxis**
  - recognized in **pharmacopoeia**

- **Drug nomenclature:**
  - Chemical name
  - **Generic name**
  - Trade or brand name (s)

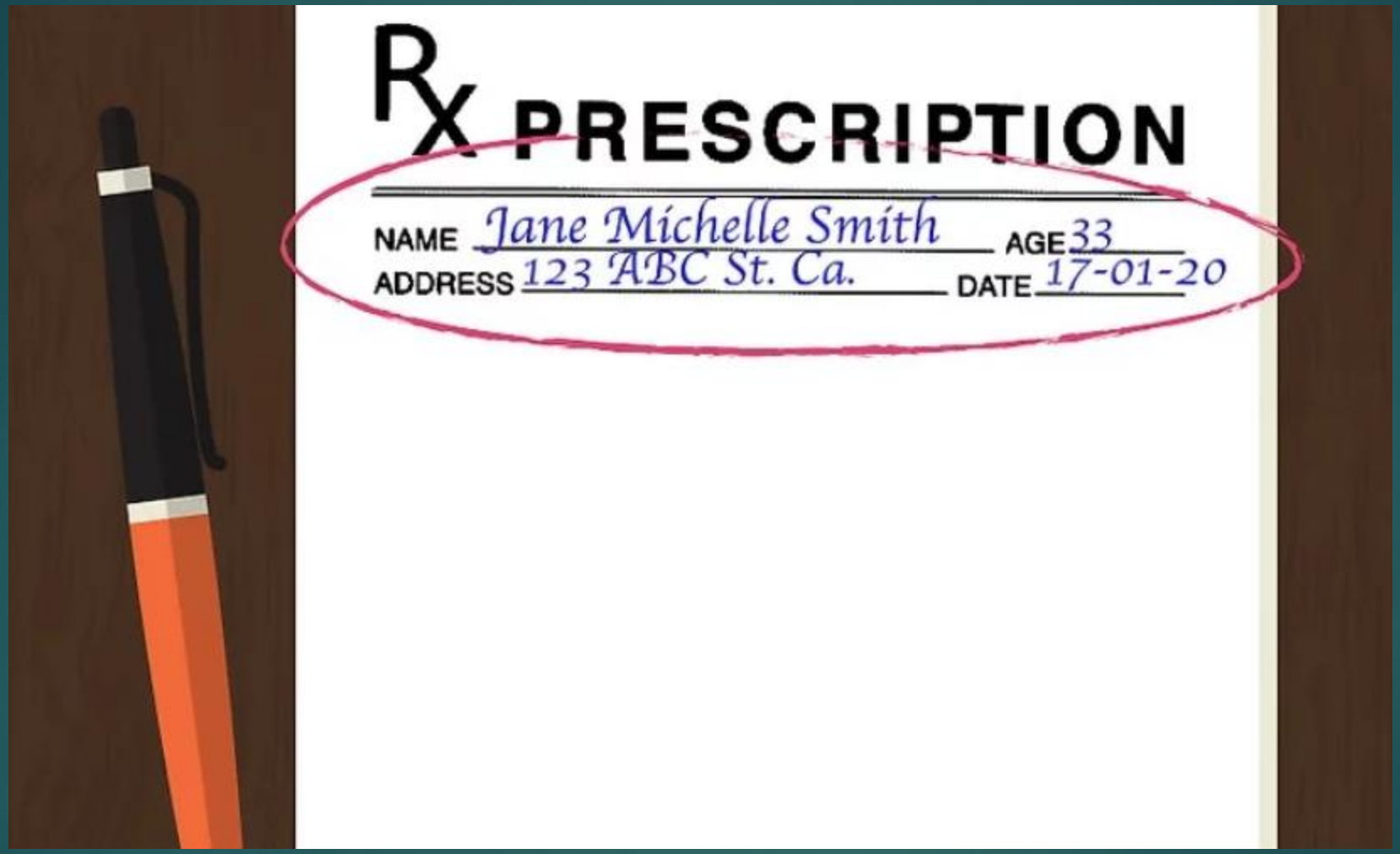
Pharmacology: science of drugs

Superscription: “Basic Information”

1. **Include at least two patient identifiers.**

Patient identifiers are pieces of information used to clarify the identity of the patient. In all settings, you must include at least two of these identifiers. **Full name** and **date of birth** are the two most common identifiers. For prescriptions fulfilled outside of a hospital, the patient's **phone number** and/or current **home address** will usually be included, as well.

One identifier isn't enough, even if you use the patient's full name. If two patients share the same name, it would be impossible to know which one the prescription refers to without any other identifier.

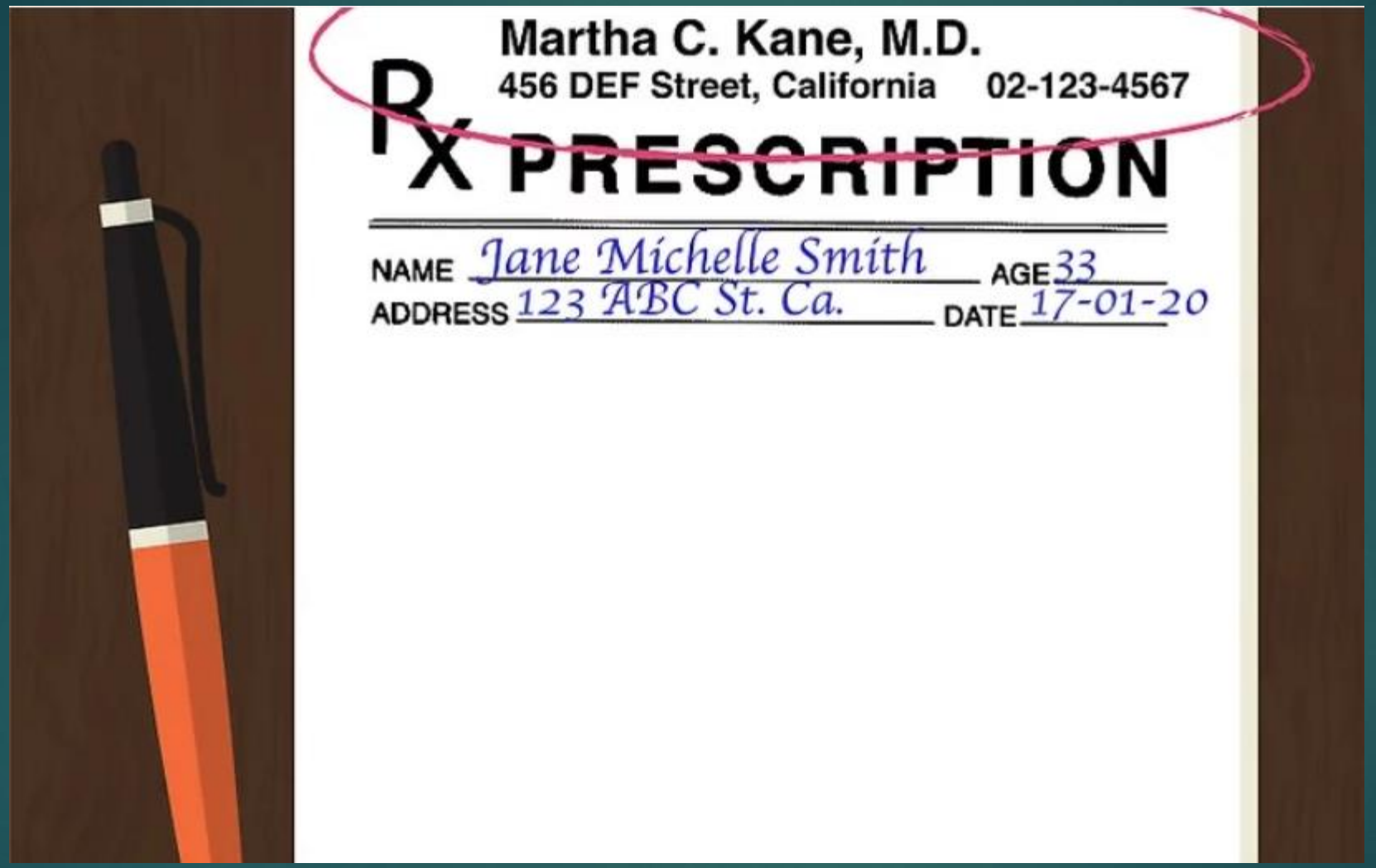

Rx PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20

2. **Provide your information.**

As the prescriber, your name and contact information must also be listed on the prescription. Include **your full name**, the **address** of your medical practice, and the **phone number** of your medical practice.

In USA: your United States Drug Enforcement Administration (DEA) number must also be included somewhere on the prescription.

In most cases, this information will already be printed on the prescription form.


Martha C. Kane, M.D.
456 DEF Street, California 02-123-4567
Rx PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20

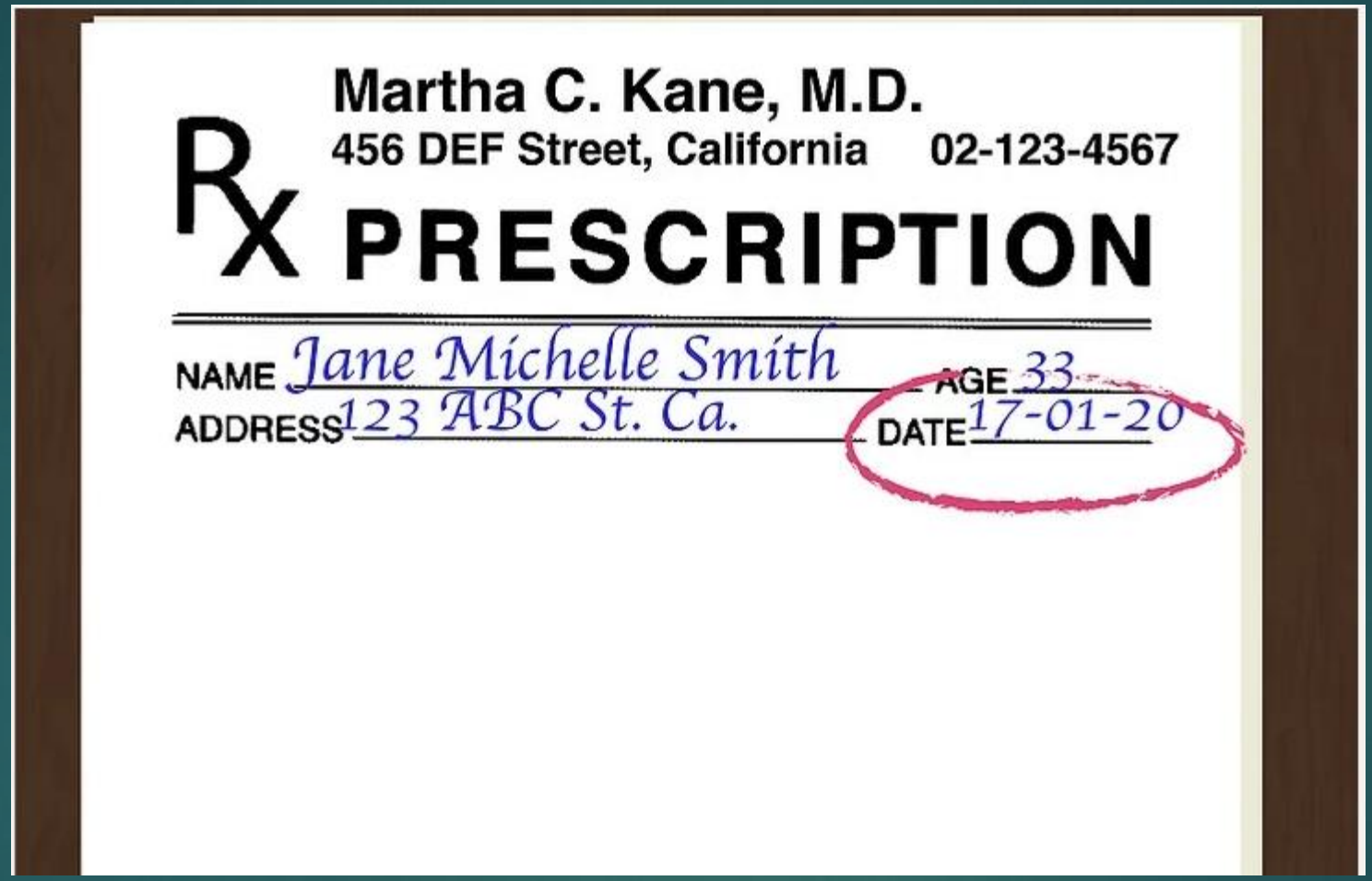
3. **Note the date of the prescription.**

Some prescriptions must be filed within a certain time period. Even when the medication being prescribed does not fall into that category, you should still include the date. Time-sensitive drugs are rated based on schedule categories. In USA

- **Schedule I drugs** have a high potential for abuse and have no legally accepted medical use within the United States.
- **Schedule II drugs** have a high potential for abuse but do have some legally accepted medical use.
- Schedule III drugs have some potential for abuse and can be used for some medical purposes.
- **Schedule IV drugs** have a relatively low potential for abuse and are legally permitted for some medical purposes.
- **Schedule V** drugs have an even lower potential for abuse and are legally permitted for certain medical purposes.

فى مصر:

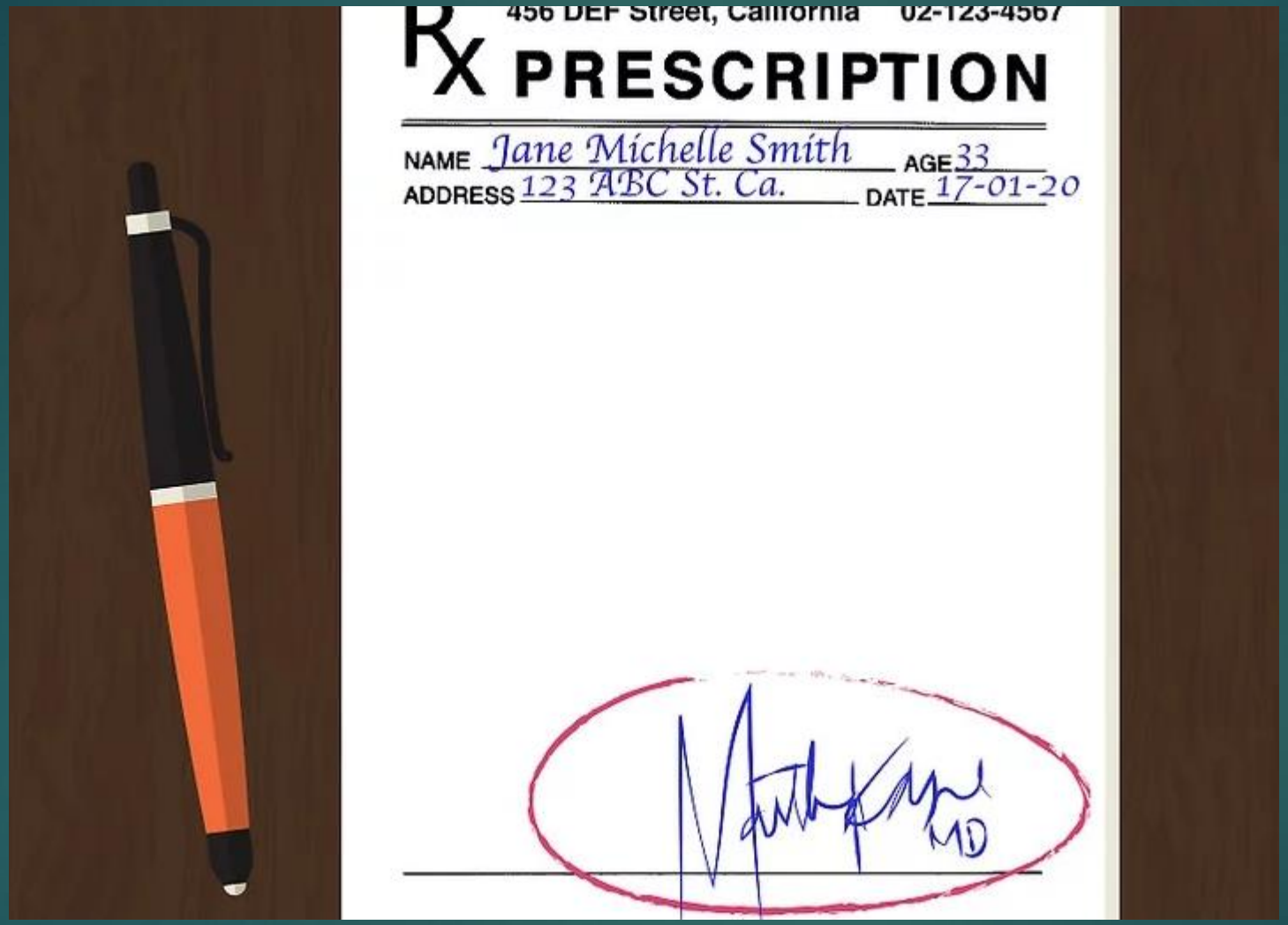
1. أدوية جدول أول (مخدرات): تصرف على روشتة مخدرات تحصل عليها من مديرية الشئون الصحية
2. أدوية جدول ثانى (المهدئات): تكتب على روشتة معتمدة من نقابة الأطباء
3. أدوية خارج الجدول:
   A. أدوية تصرف على روشتة عادية
   B. أدوية تصرف بدون روشتة (OTC)


Martha C. Kane, M.D.
456 DEF Street, California 02-123-4567
Rx PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20

4. **Sign the prescription.**

You will need to sign each prescription before it can be considered valid. Your signature will usually go at the bottom of the form, regardless of whether or not there is a specific line for it there. It is strongly recommended that you write out the rest of the prescription and sign your name last.

Doing so prevents unfinished or blank prescriptions from falling into the wrong hands.

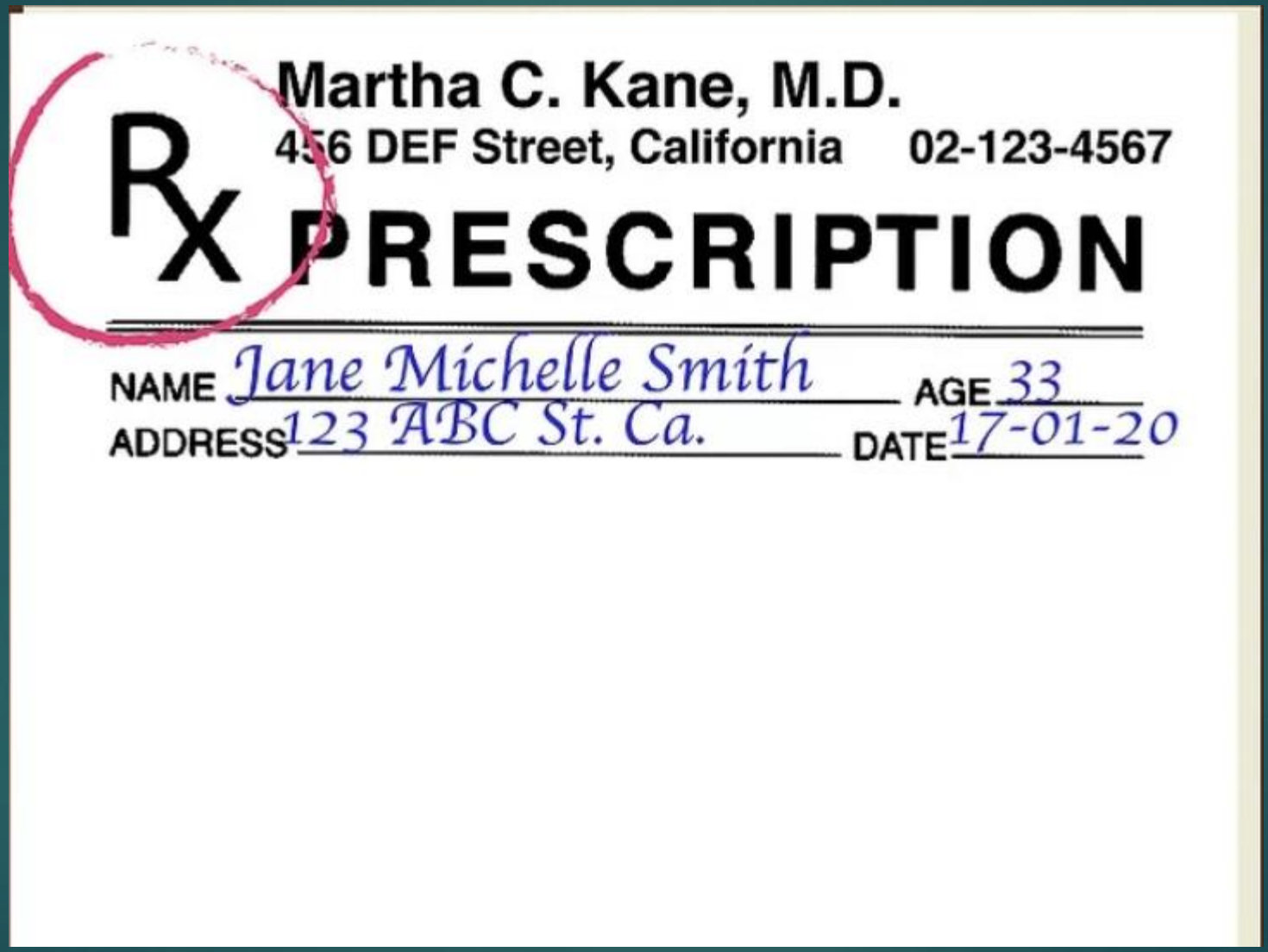

456 DEF Street, California 02-123-4567
Rx PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20
MD

Inscription

1. **Display the "Rx" symbol.**

"Rx" is the symbol for "superscription." Write it just before you write out your instructions for the medication itself. On most prescription forms, the "Rx" is already printed.

Write the inscription information immediately after this symbol. The inscription includes all of the information about the specific drug you want to prescribe.



Martha C. Kane, M.D.
456 DEF Street, California 02-123-4567

Rx PRESCRIPTION

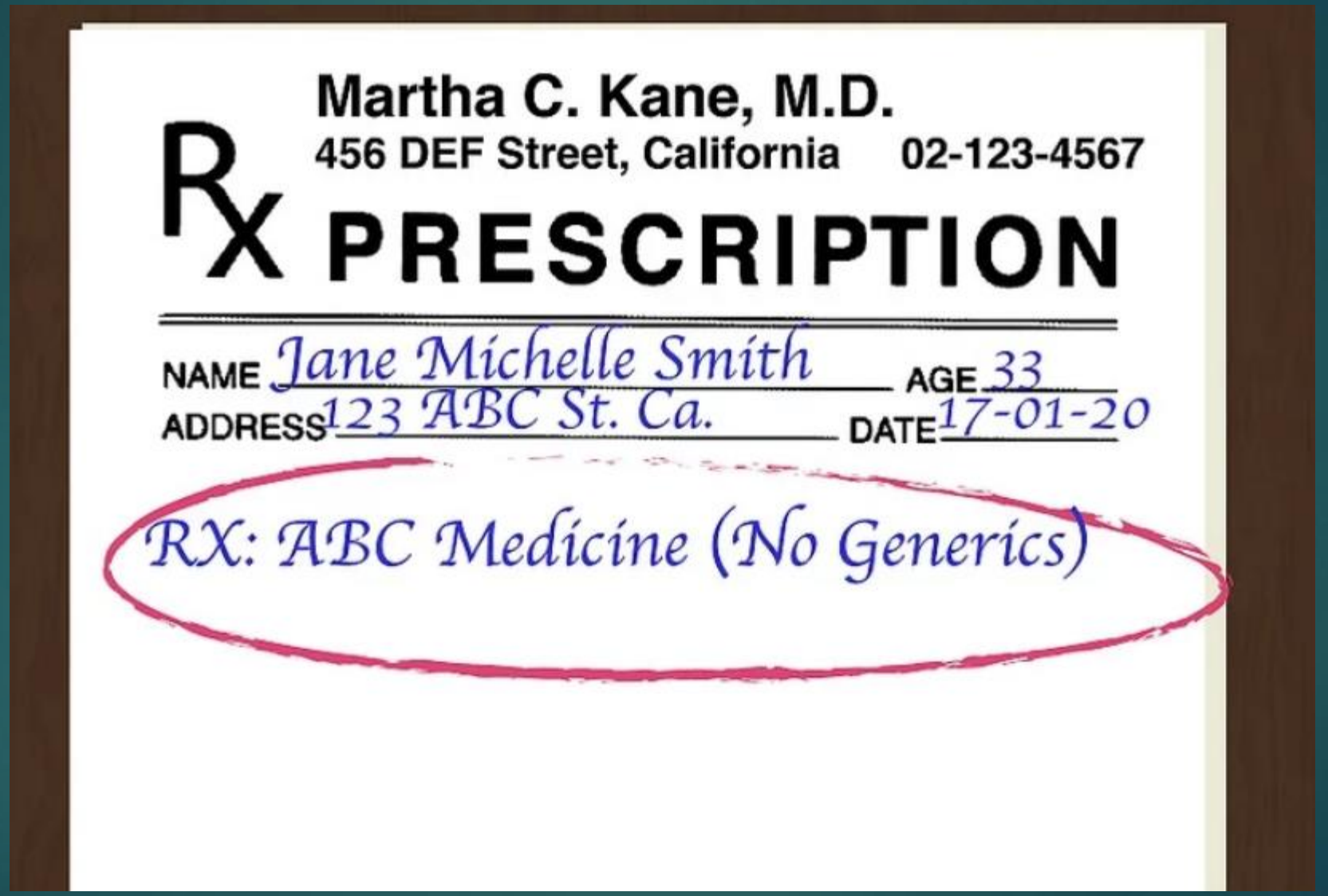
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20

2. **Write the medication.**

You should typically use the **generic**, non-proprietary name of the drug instead of the name brand.

Use the name **brand** of the drug only when you specifically wish to prescribe the name brand. Keep in mind that doing so may make the prescription more expensive for the patient.

If you want to prescribe the name brand, you should also include a note on the prescription reading "No Generics." On most prescription forms, there will be a "Brand Name Only" or "No Generics" box you have the option of checking for this purpose.

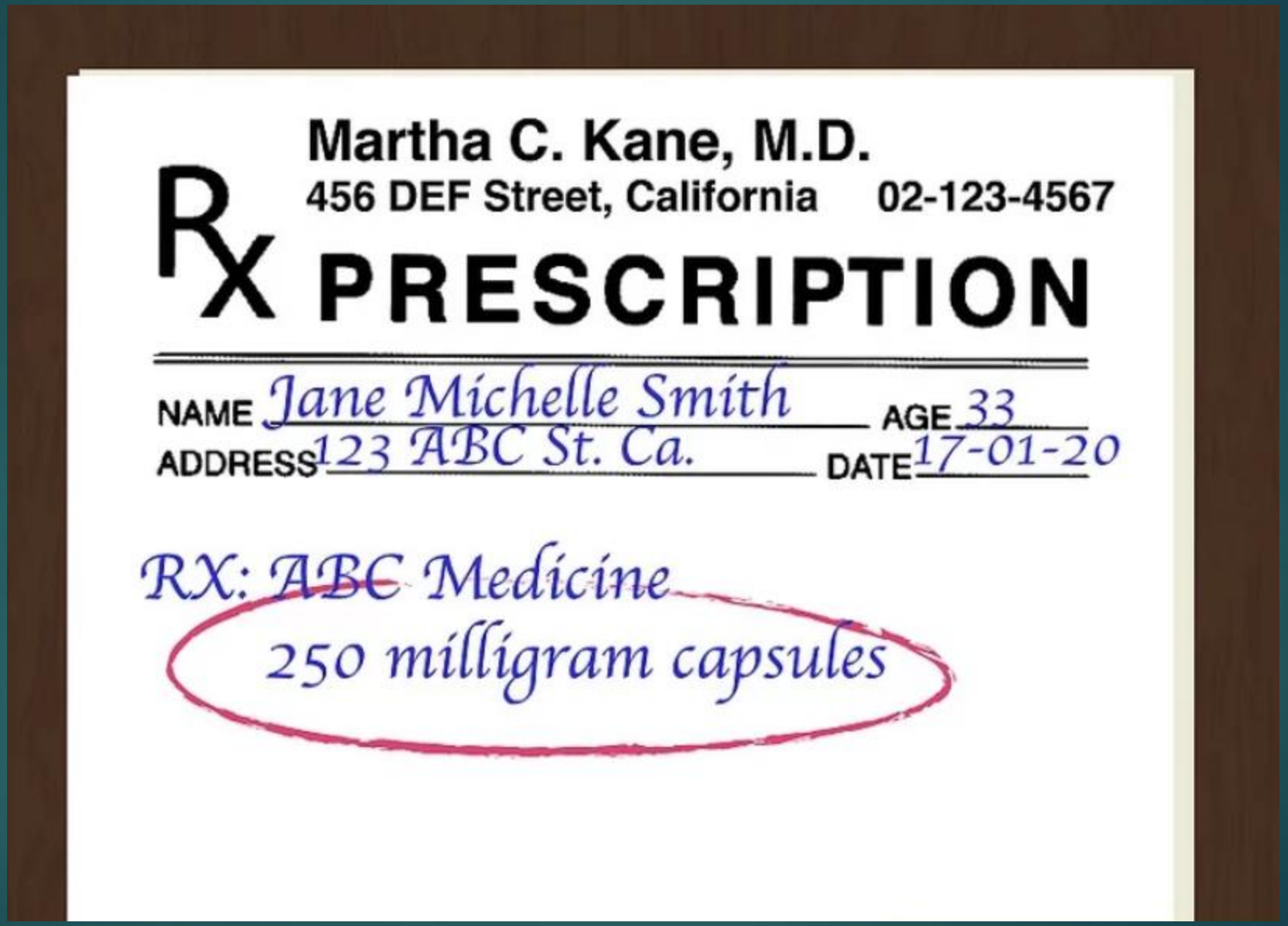

Martha C. Kane, M.D.
456 DEF Street, California 02-123-4567
Rx PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20
RX: ABC Medicine (No Generics)

3. **Mention the strength.**

Most medications come in multiple strengths, so you must mention the strength you wish to prescribe immediately after the name of the medication.

The strength amount should be indicated in milligrams for tablets and suppositories and milliliters for fluids.

You can write words instead of abbreviations to avoid possible misunderstandings.

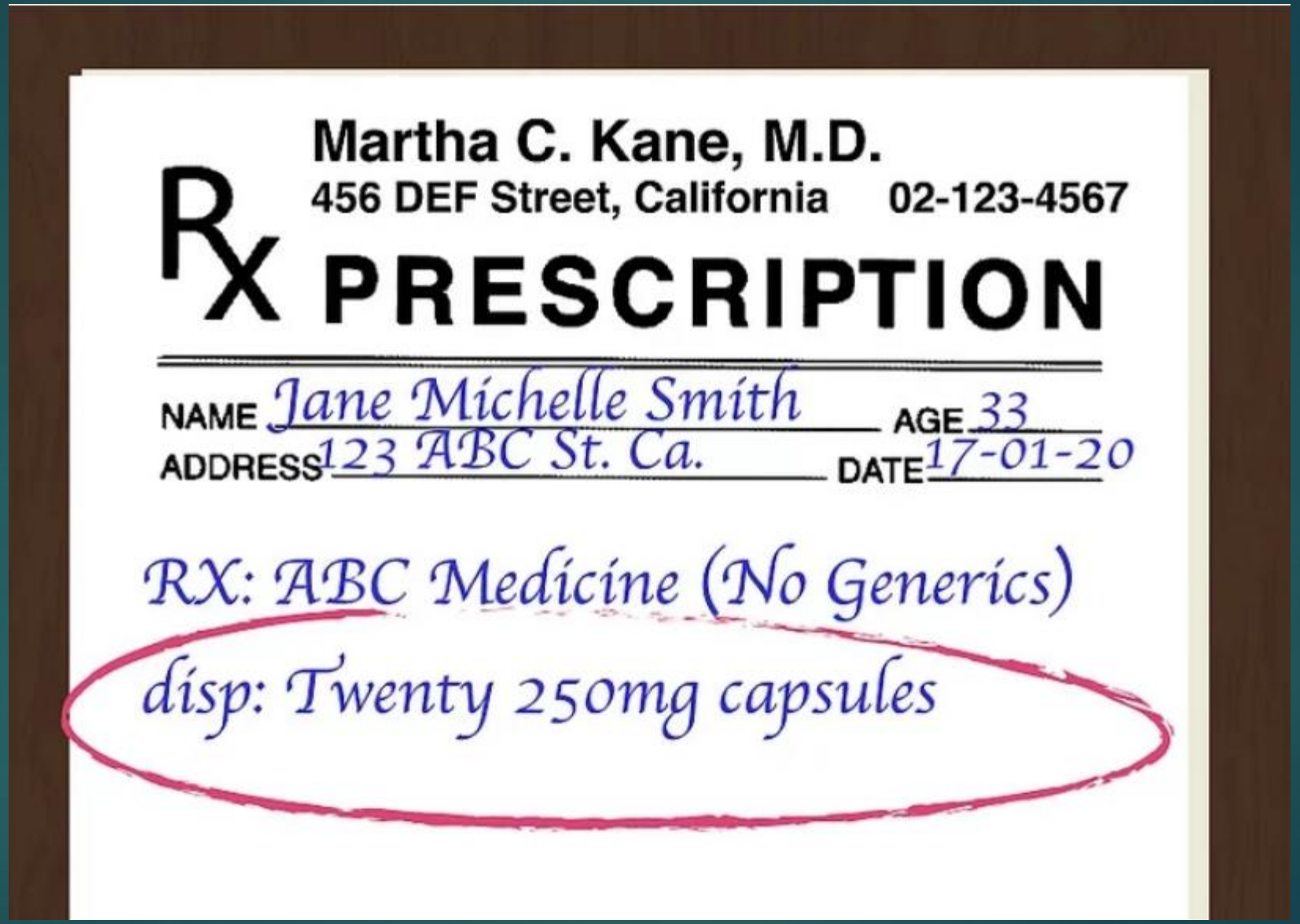

Martha C. Kane, M.D.
456 DEF Street, California 02-123-4567
Rx PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20
RX: ABC Medicine
250 milligram capsules

Subscription

1. **Include the prescription amount.**

Tell the pharmacist exactly how much of the medication should be filled and passed to the patient. This information should usually be preceded by an appropriate heading, such as "dispense," "disp," "#," or "how much."

Include the specific bottle size or number of tablets/capsules. Spell the numbers out to avoid possible miscommunication.

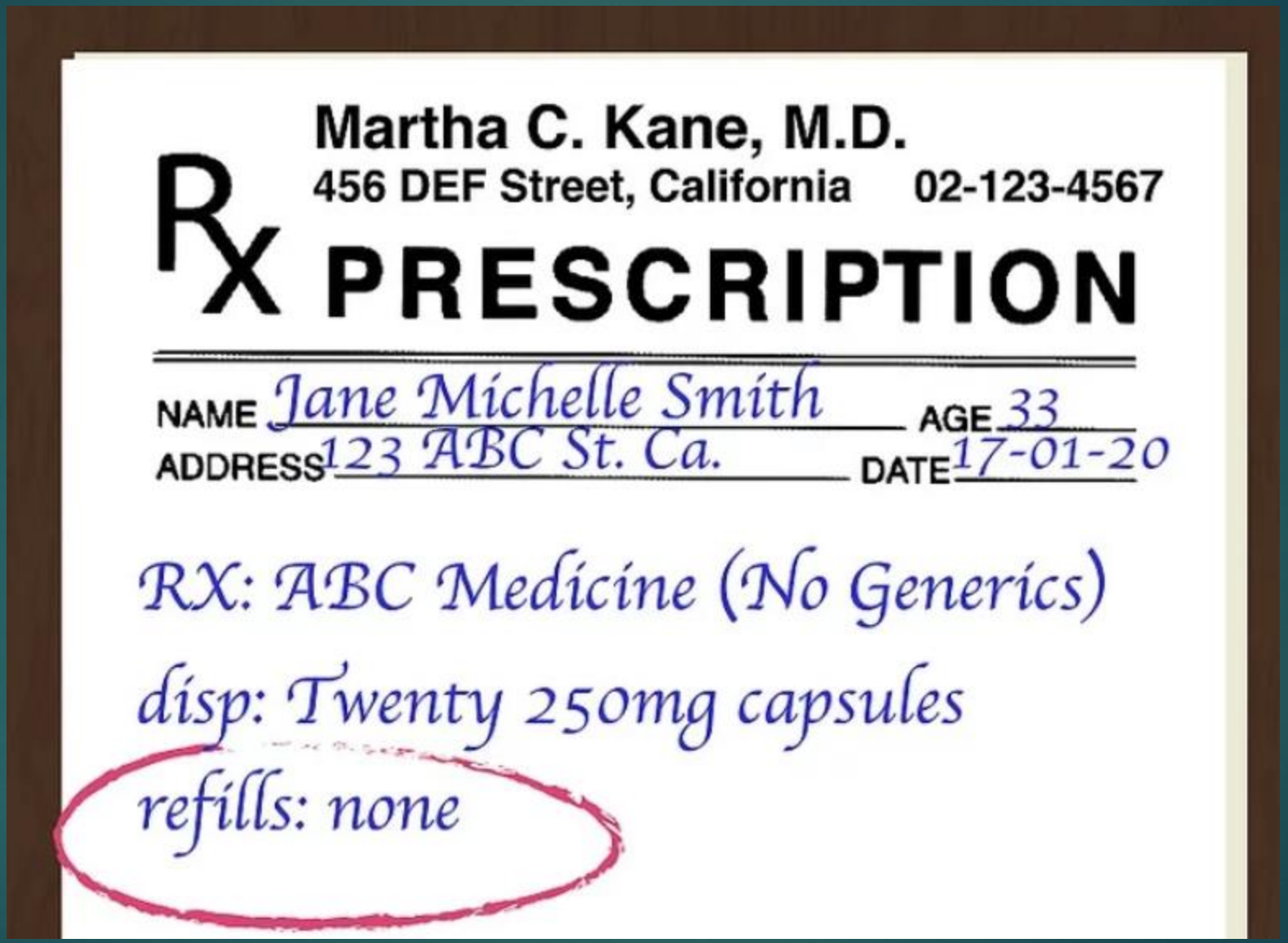

Martha C. Kane, M.D.
456 DEF Street, California 02-123-4567
Rx PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20
RX: ABC Medicine (No Generics)
disp: Twenty 250mg capsules

2. Note the number of permitted refills.

For medications that treat a chronic condition or other similar reasons, you may wish to permit a certain number of refills before another prescription will be required. Only allow additional refills when the patient will need the exact same prescription multiple times.

For example, you might wish to prescribe a year's worth of oral contraceptives, yet each fulfillment of the prescription might only provide a month's worth. On the prescription form, write "Refills 11" to indicate that eleven refills are permitted after the first fulfillment. After the final refill runs out, the patient will need a new prescription before any additional medication can be obtained.

If you do not wish to permit any refills, write "Refills 0" or "Refills none" to indicate as much. Doing so reduces the risk of possible tampering.

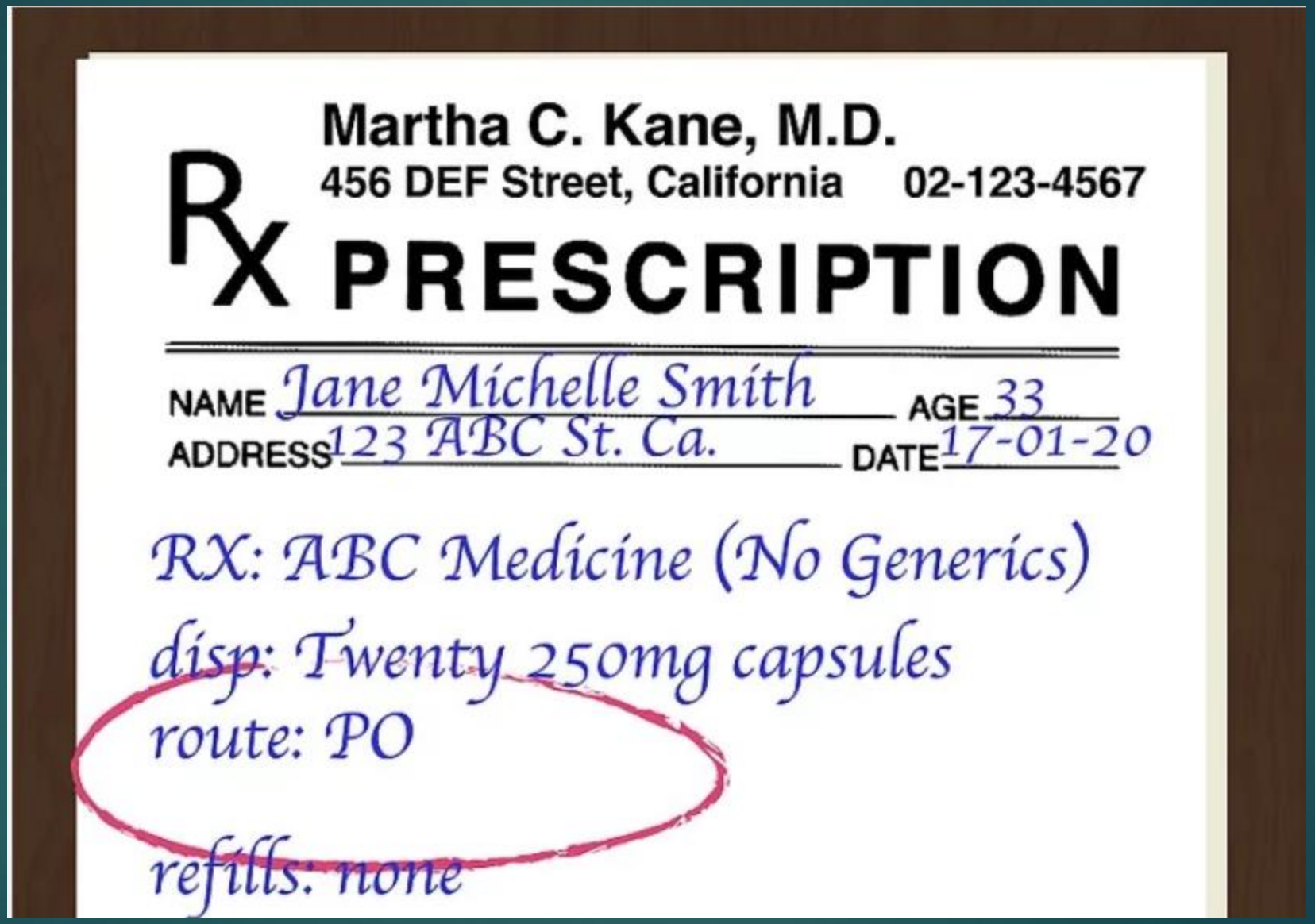

Martha C. Kane, M.D.
456 DEF Street, California 02-123-4567
Rx PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20
RX: ABC Medicine (No Generics)
disp: Twenty 250mg capsules
refills: none

Patient Use Directions فى مصر تكتب باللغة العربية

1. **Specify the route.** The route is the method used to take the medication prescribed. When writing the route, you can mention the instructions using either the accepted English term or the corresponding Latin abbreviation.

Common options include:

- By mouth (PO)
- Per rectum (PR)
- Intramuscular (IM)
- Intravenous (IV)
- Intradermal (ID)
- Intranasal (IN)
- Topical (TP)
- Sublingual (SL)
- Buccal (BUCC)
- Intraperitoneal (IP)

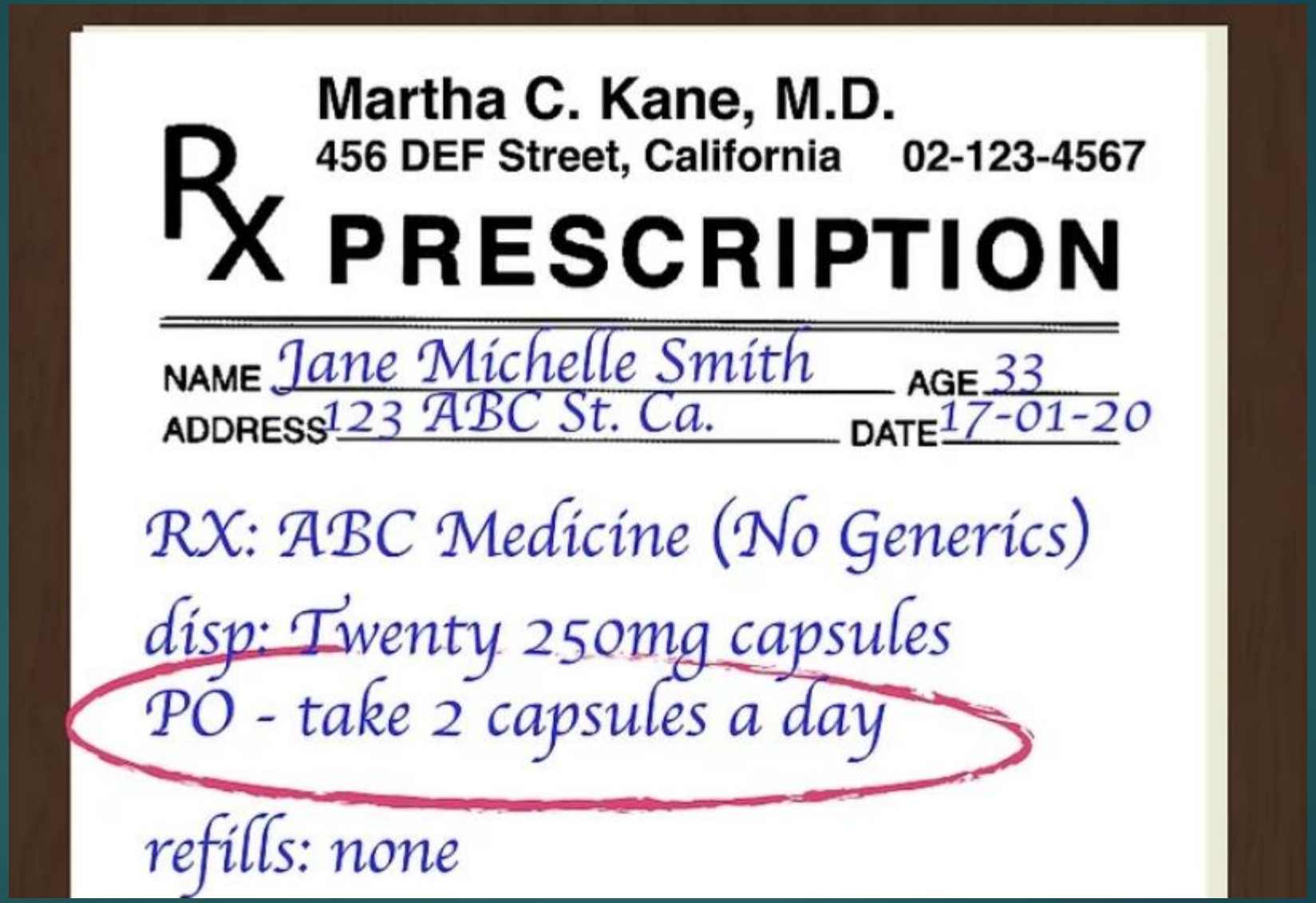

Martha C. Kane, M.D.
456 DEF Street, California 02-123-4567
Rx PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20
RX: ABC Medicine (No Generics)
disp: Twenty 250mg capsules
route: PO
refills: none

2. **State the dosage amount.**

State how much of the medication the patient should use each time he or she takes it.

These instructions will be transferred to the prescription label once it is fulfilled.

For instance, you might write something like "one 30 milligram tablet" or "30 milliliters.

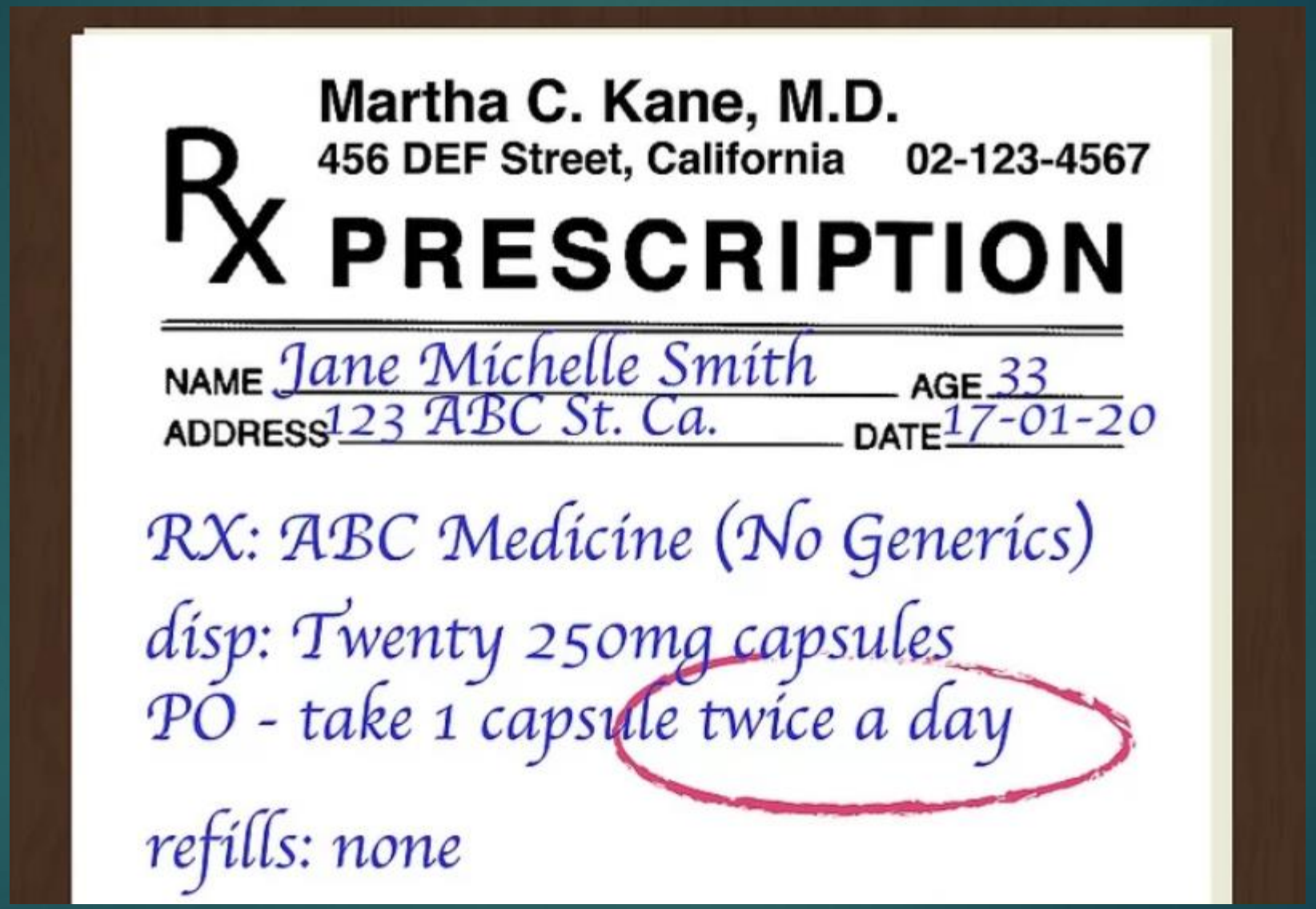

Martha C. Kane, M.D.
456 DEF Street, California 02-123-4567
Rx PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20
RX: ABC Medicine (No Generics)
disp: Twenty 250mg capsules
PO - take 2 capsules a day
refills: none

3. Indicate the frequency.

The frequency describes when and how often the medication should be taken. It is strongly recommended that you write out the frequency in full rather than using abbreviations. In fact, a medication that must be used "daily" or "every other day" must be written out in full. Abbreviations for these frequencies are prohibited.

Other frequency abbreviations can be used, but it is still recommended that you spell out the instructions instead of using the abbreviated form. Several common options include:

- Twice a day (BID)
- Four times a day (QID)
- Every four hours (Q4H)
- Every week (QWK)
- Three times a day (TID)
- Every bedtime (QHS)
- Every four to six hours (Q4-6H)
- Three times a day after meals (TDS)



Martha C. Kane, M.D.
456 DEF Street, California 02-123-4567

Rx PRESCRIPTION

NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20

RX: ABC Medicine (No Generics)

disp: Twenty 250mg capsules
PO - take 1 capsule twice a day

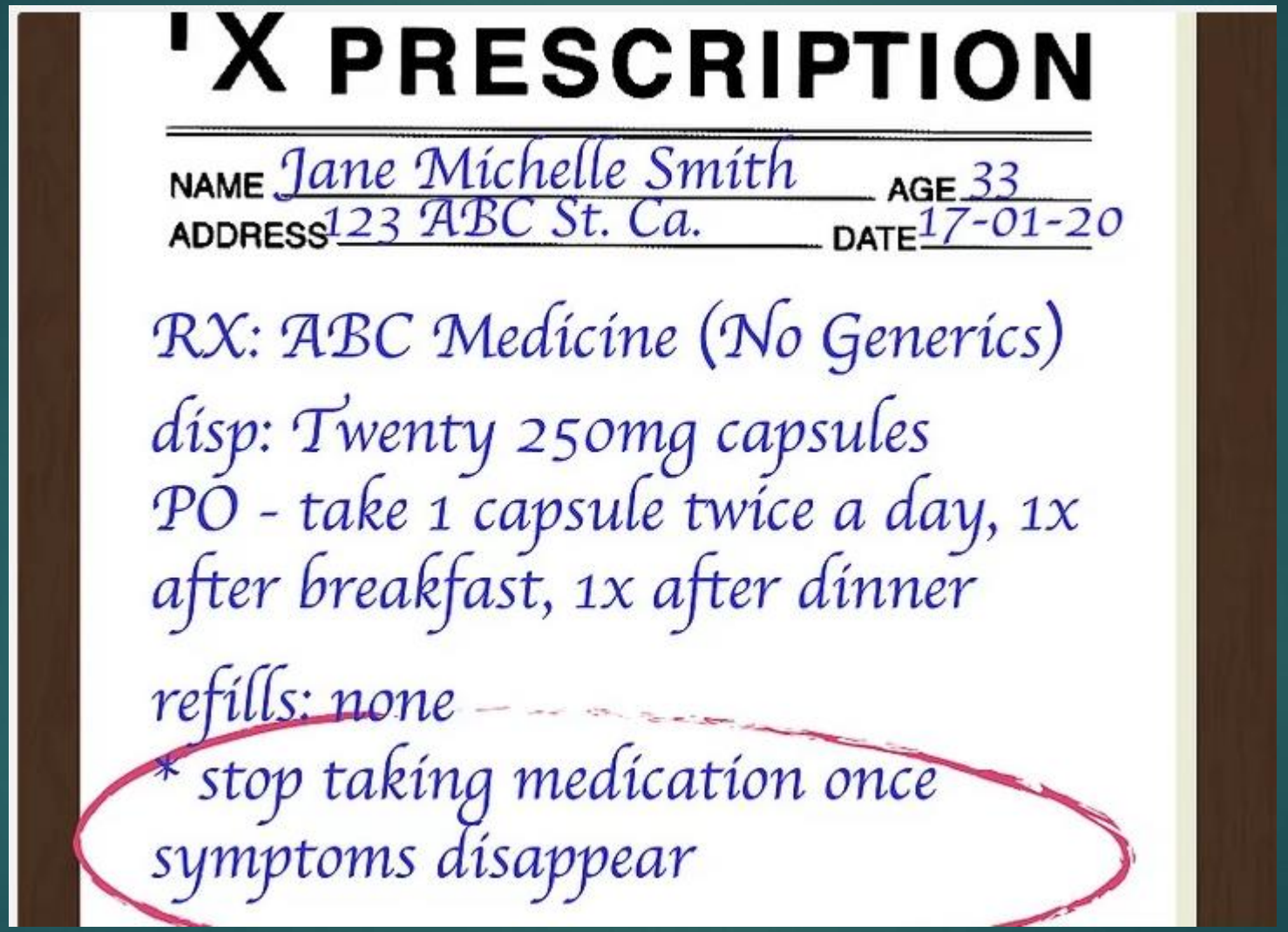
refills: none

4. **Write when to discontinue use.**

Most medications must be taken until the drug runs out.

In some cases, however, the patient should stop taking the medication once his or her symptoms disappear.

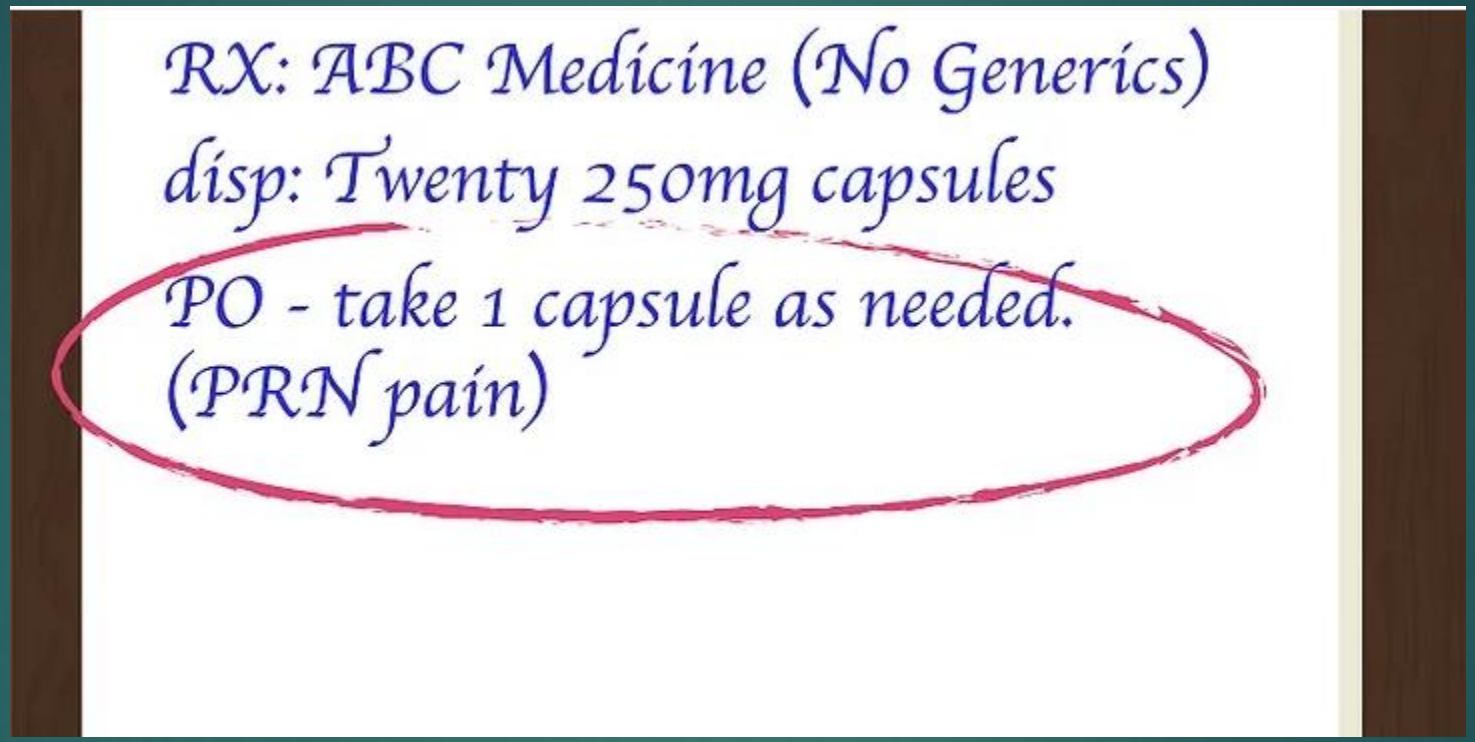
You should specifically write which is the case on the prescription form.


℞ PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20
RX: ABC Medicine (No Generics)
disp: Twenty 250mg capsules
PO - take 1 capsule twice a day, 1x after breakfast, 1x after dinner
refills: none
* stop taking medication once symptoms disappear

5. **Consider including the diagnosis.**

When a medication should only be used on an "as needed" basis, you should include a brief diagnosis or reason for taking the medication.

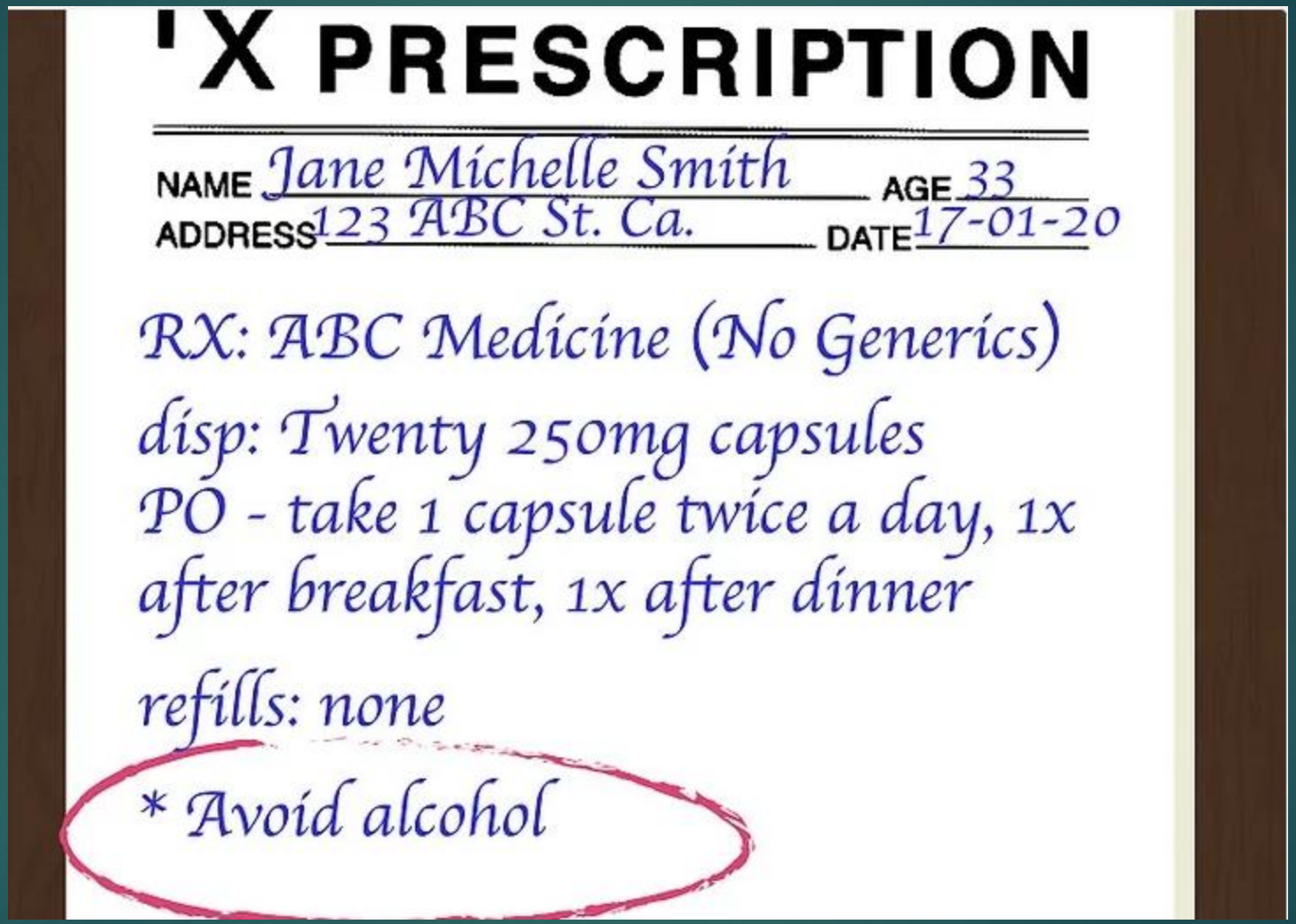
Specify this diagnosis with the abbreviation "PRN." For example, the statement for a pain medication might read "PRN pain."


RX: ABC Medicine (No Generics)
disp: Twenty 250mg capsules
PO - take 1 capsule as needed.
(PRN pain)

6. **Mention any other special instructions.**

Occasionally, there might be a special instruction that needs to go on the label. Let the pharmacist know to include it by specifically writing the instruction on the prescription form. A few common examples include:

- "Take with food"
- "Avoid alcohol"
- "Keep refrigerated"
- "Do not freeze"
- "For external use only"
- "Shake before instillation"


℞ PRESCRIPTION
NAME Jane Michelle Smith AGE 33
ADDRESS 123 ABC St. Ca. DATE 17-01-20
RX: ABC Medicine (No Generics)
disp: Twenty 250mg capsules
PO - take 1 capsule twice a day, 1x after breakfast, 1x after dinner
refills: none
* Avoid alcohol

Warnings

1. To reduce the risk of tampering or miscommunication, write prescriptions in ink or indelible pencil. They may also be typewritten.
2. Make sure that all prescriptions are written clearly and legibly to avoid errors in dosage. Some errors can be deadly, so it is crucial that you do what you can to prevent them.
3. Only write a prescription if you are authorized to do so. In most cases, this means that you must be registered with the DEA فى مصر نقابة الأطباء or specially exempted from registration.