ILLUMINATIONS

Using virtual patients to integrate physiology, pathophysiology, and pharmacology in preclinical teaching

Persoulla Nicolaou,1 Peter McCrorie,1 and Stella A. Nicolaou2

1Department of Basic and Clinical Sciences, Medical School, University of Nicosia, Nicosia, Cyprus; and 2Department of Life and Health Sciences, University of Nicosia, Nicosia, Cyprus

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INTRODUCTION

Traditionally, pharmacology has been taught in isolation of other disciplines using lecture-based learning, which often lacks clinical relevance and may predispose the learner to information overload. While didactic teaching may promote a culture of passive learning, educators have advocated its merits in conveying consistent information to learners.

To address the limitations of traditional teaching and promote active learning, medical educators have advocated the use of virtual patients (VPs) (3, 4). VPs are interactive computer-based patient scenarios, where the learner can choose how to proceed in the care of a VP. Importantly, the use of VPs is aimed at helping students gain and apply knowledge in a safe environment, which they can subsequently apply to clinical practice. Interestingly, VP scenarios are generally used in clinical years to cultivate the skills needed by a junior doctor, including history-taking, diagnostic reasoning, and management in a range of medical specialties, for example, occupational medicine, surgery, and internal medicine (1, 5). Conversely, the use of VPs in preclinical years and in specific preclinical disciplines, including pharmacology, is not well-described in the literature. The integrative nature of pharmacology provides medical educators with the opportunity to not only teach the underlying basis of therapeutics, but to also facilitate integration of knowledge in other disciplines, such as physiology and pathophysiology. VPs represent an ideal conduit to achieve this.

To combine the merits of traditional teaching with those of VPs, we have utilized both methodologies in the course of Systematic Pharmacology I. This course was delivered to 31 students in the third year of a six-year medical program, at the University of Nicosia. Most learners join our program on successful completion of high school and thus have no higher education qualifications. Learners generally have a basic science background (e.g., in biology and/or chemistry). The pharmacology course comprises traditional lectures (3 h/wk), followed by a 1-h tutorial session. Lectures were delivered once to the entire cohort. For the tutorials, students were separated into two groups to allow more interactivity. Both groups received the same teaching. Six different VP cases were delivered over the semester. The VP cases were designed to allow students to apply physiological and pathophysiological concepts to pharmacology, thus helping them to make rational prescribing decisions, decipher mechanisms of drug action, and identify adverse effects. The platform used to deliver the cases was OpenLabyrinth (2). This paper describes one of the cases to allow replication and demonstrate proof of concept for further case development by other educators. The case may also be adapted to make it suitable for other disciplines, e.g., physiology. The remaining five cases can be provided to educators upon request.

Description of the VP Case and Process

In this VP-based tutorial, students follow the case of Sam Davis, which unfolds over six different parts. The case is designed to take a different pathway, based on student choices. The following steps are applied in each of the six parts (see Fig. A2), with the tutor acting as a facilitator rather than a teacher:

1. One of the students reads out the information.
2. Students highlight the important findings and clarify unknown terms.
3. A question is revealed, and students are prompted to discuss it, before revealing the five different options/pathways.
4. Students reach a consensus and choose one of the available pathways. If students follow a wrong pathway, the case progresses to reveal the consequences of their action. Students are subsequently provided with the opportunity to choose again and return to the correct pathway.

The case is described briefly below. The full case is provided in the appendix.

Part 1: Patient Presentation. Students are told that they are final-year medical students, on a medicine clinical placement, when Sam presents to Dr. Raj’s clinic. This first part concludes with the patient’s diagnosis, i.e., Grave’s disease (see appendix). An important implication is that Sam is 8 wk pregnant. The tutor prompts students in this part of the case to explain Sam’s presentation, based on the physiological function of thyroid hormones. Subsequently, students are prompted to discuss the underlying pathophysiological mechanisms of the disease before describing its pharmacological management and making an appropriate prescribing decision, i.e., propylthiouracil (PTU).

Part 2: Mechanism of action of PTU. In part 2, students are presented with a diagram of thyroid hormone synthesis and release; with each step labeled with a capital letter (A–F), as
shown in Fig. A1 of the appendix. This provides students with the opportunity to revise the molecular mechanisms involved in thyroid synthesis and secretion and link the inhibition of this pathway to the pharmacological effects of PTU (i.e., inhibition of thyroid peroxidase-catalyzed reactions, including iodination and coupling, and inhibition of de-iodination of T4).

Part 3: Emergency management of thyroid storm. The case continues to unfold with Sam ending up in the Emergency Department, where thyroid storm is diagnosed. Students discuss the underlying mechanisms for this acute emergency and are asked to choose the most appropriate management for Sam. This part of the case facilitates rational prescribing practice, based on treating the underlying pathology. It is emphasized that thyroid storm is an acute emergency and needs to be treated aggressively using a number of drugs, including PTU, propranolol, hydrocortisone, and iodine solution. Once Sam is managed accordingly, the case progresses, with Sam’s medication being switched to methimazole in the second trimester. This prompts students to discuss considerations for prescribing in pregnancy.

Part 4: Labor. Sam gives birth to a healthy baby girl, but she is concerned that her milk output is low. Students are asked to choose a hormone-modulating drug to increase milk output. The case allows students to revisit not only the neurophysiology and effects of dopamine antagonism, which is the correct response, but also the function of other hormones, including vasopressin and somatostatin.

Part 5: Adverse drug reaction to methimazole. In part 5, students follow Sam’s progress 2 yr later. She experiences an idiosyncratic drug reaction, i.e., neutropenia, due to methimazole. This facilitates discussion on adverse effects and the underlying mechanisms for this hypersensitivity reaction. Sam is advised to undergo radioactive iodine treatment, and students are prompted to discuss thyroid replacement therapy, with levothyroxine, which is the correct response. This part allows discussion about active thyroid hormones in normal physiology, implications for route of administration, and cost.

Part 6: Epilogue. The case wraps up with Sam doing very well on her current treatment regimen. However, she poses a question about her baby’s risk for developing Grave’s disease. This prompts students to discuss the underlying genetics that may contribute to this pathology.

Effectiveness of VP Case

This type of tutorial may provide a useful educational tool to prepare medical students for clinical practice early on, while at the same time allowing them to revisit and integrate basic principles across disciplines. Importantly, this approach promotes active engagement and group work, with the tutor acting as a facilitator rather than a teacher. Students get feedback on their choices, in the form of Dr. Raj, the physician to whom they are attached, who features in the case (appendix). Thus they can learn from their mistakes from the case itself rather than the teacher. Feedback on the usefulness of the VP tutorials was obtained by two faculty members, who acted as peer reviewers. The first reviewer commented that the cases provided a much-needed clinical context with the group immediately being engaged with the process. Furthermore, he commended the facilitation of the session by the tutor. The reviewer noted that some students appeared disengaged at times, which is not unusual with problem-based learning tutorials. Similarly, the second reviewer also noted that most students were very active and participative. Importantly, both reviewers provided useful feedback for the setup of the session. In particular, one noted that the session would be better facilitated in a circle or around a table rather than a traditional classroom, while the other reviewer suggested running the tutorials in even smaller groups. Importantly, students provided positive feedback on the tutorials. One student commented that she could get practice questions from several resources, such as question banks, but the exposure to VPs and its usefulness was one that could not be easily replicated. It was gratifying to hear one of our students, saying, “This is what happened to Sam,” when we encountered the same concept in a future session in class. It was also interesting to observe the students’ response to taking the wrong pathway. Following the wrong pathway and being provided with feedback was perhaps the most useful and rewarding aspect of the cases. Future studies could explore further the potential benefits of VP-based tutorials.

APPENDIX: CASE NAME: SAM DAVIS

The complete case for Sam Davis is described below to allow replication by other educators. The optimal pathway is in bold. The case map is shown schematically in Fig. A2, with the optimal pathway shaded.

Part 1: Patient Presentation

You are a final-year medical student on a medicine clinical placement. Dr. Raj, a consultant in Endocrinology, is the supervising doctor.

Sam, a 32-yr-old woman, presents to the clinic that afternoon because of anxiety, palpitations, and easy fatigability. She also reports that she has difficulty sleeping at night, and that her husband complains that she is keeping the house very cool. She is 8 wk pregnant, and, therefore, she initially attributed these symptoms to her pregnancy.

She goes on to tell you that she recently consulted her ophthalmologist because of redness and watering of the eyes. Eye drops were not

Fig. A1. Thyroid hormone synthesis and release. D1/D2, deiodinase 1 and 2; DIT, diiodotyrosine; MIT, monoiodotyrosine; NIS, sodium-iodide symporter; TG, thyroglobulin; TPO, thyroid peroxidase. Steps A–F are shown.
helpful. Furthermore, in the last 2 mo she has lost ~11 kg. Sam’s gynecologist thought it was best that she see an endocrinologist. On physical examination, her pulse rate is 100 beats/min and her thyroid is slightly enlarged. Conjunctivae are red, and she has a stare. Following further investigations, a diagnosis of Grave’s disease is reached.

Which drug would you prescribe for Sam?

A. Guanethidine. You prescribe guanethidine eye drops for Sam. She thanks you for your help. Two weeks later, Sam starts to feel very unwell. She is sweating profusely, has a fever, and her heart is racing. Her husband takes her to the Emergency Department, where thyroid storm is diagnosed.

Sam is treated accordingly and stabilized. The attending physician establishes that Sam was only taking guanethidine for her hyperthyroidism. He advises Sam to go back to her endocrinologist to reconsider her pharmacological management.

Please go back and reconsider.

B. Iodine (isotope 131). You inform Sam that you think radioactive iodine is more likely than other therapies to help control her symptoms. Dr. Raj looks to you and is concerned that you would recommend this treatment for a pregnant woman.

Please go back and reconsider.

C. Methimazole. You inform Sam that you recommend treatment with an anti-thyroid drug rather than radioactive iodine, as radioactive iodine may harm the baby. Dr. Raj agrees with your decision not to use radioactive iodine, but she is a little concerned about your choice of anti-thyroid drug, in the first trimester of pregnancy, as methimazole has been associated with teratogenic effects in this setting.

Please go back and reconsider.

D. Propranolol. Dr. Raj agrees with you that beta-blockers may be useful drugs in some patients with Grave’s disease as cardiac function and electrical conductance may be increased. However, she does not agree that this is the best drug for Sam in the first instance, since you have not prescribed a drug to address the root of the problem, i.e., increased activity of the thyroid gland.

Please go back and reconsider.

E. Propylthiouracil. You inform Sam that her pregnancy precludes her from radioactive iodine treatment at this point in time, and that propylthiouracil is the safest option right now. Dr. Raj agrees with you. She asks you whether you remember the mechanism of action of this drug.

**Part 2: Mechanism of Action of PTU**

Refer to the diagram (Fig. A1) and identify the steps inhibited by this drug.

A. Steps A, B, and D. Are you sure? Propylthiouracil works by inhibiting thyroid peroxidase-catalyzed reactions. It has also been implicated in inhibition of de-iodination of T4.

Please go back and reconsider.

B. Steps A, B, and E. Are you sure? Propylthiouracil works by inhibiting thyroid peroxidase-catalyzed reactions. It has also been implicated in inhibition of de-iodination of T4.

Please go back and reconsider.

C. Steps A, B, and C. Are you sure? Propylthiouracil works by inhibiting thyroid peroxidase-catalyzed reactions. It has also been implicated in inhibition of de-iodination of T4.

Please go back and reconsider.

D. Steps B, C, and F. Excellent! Propylthiouracil works by inhibiting thyroid peroxidase-catalyzed reactions. It has also been implicated in inhibition of de-iodination of T4.

Please go back and reconsider.

E. Steps B, C, and E. Are you sure? Propylthiouracil works by inhibiting thyroid peroxidase-catalyzed reactions. It has also been implicated in inhibition of de-iodination of T4.

Please go back and reconsider.

**Part 3: Emergency Department**

Over the next month, Sam regularly forgets to take her medication. She puts that down to “pregnancy brain” and is not too concerned about it. Later that evening, Sam starts to feel very unwell. She is sweating profusely, has a fever, and her heart is racing. Her husband takes her to the Emergency Department, where thyroid storm is diagnosed.

What is the most appropriate management for Sam?

A. Propylthiouracil, propranolol, and hydrocortisone. The doctor on call agrees that Sam will need an anti-thyroid drug. He agrees that propylthiouracil is a good choice, as it may exert rapid effects due to inhibition of de-iodination of T4. He also agrees that
propranolol should be administered to counteract sympathetic overactivity. Hydrocortisone is also useful to suppress the immune-mediated responses in Grave’s disease.

The doctor also recommends that iodine solution is administered as it may temporarily inhibit release of thyroid hormones, with beneficial effects in this acute emergency.

**FURTHER DEVELOPMENT.** Sam is stabilized and discharged. She is very disturbed by the outcome of her noncompliance with her medication and decides to set a daily alarm on her phone to remind her to take her medication, which is now switched to methimazole, as she is well into her second trimester.

**B. Propylthiouracil, propranolol, hydrocortisone, and iodine solution.** The doctor on call agrees that Sam will need an anti-thyroid drug. He agrees that propylthiouracil is a good choice, as it may exert rapid effects due to inhibition of de-iodination of T4. He also agrees that propranolol should be administered to counteract sympathetic overactivity. Hydrocortisone is also useful to suppress the immune-mediated responses in Grave’s disease. Finally, he also agrees that iodine solution should be administered as it may temporarily inhibit release of thyroid hormones.

**FURTHER DEVELOPMENT.** Sam is stabilized and discharged. She is very disturbed by the outcome of her noncompliance with her medication and decides to set a daily alarm on her phone to remind her to take her medication, which is now switched to methimazole, as she is well into her second trimester.

**C. Propylthiouracil and propranolol.** The doctor on call agrees that Sam will need an anti-thyroid drug. He agrees that propylthiouracil is a good choice, as it may exert rapid effects due to inhibition of de-iodination of T4. He also agrees that propranolol should be administered to counteract sympathetic overactivity.

The doctor also recommends that you also administer hydrocortisone to suppress the immune-mediated responses in Grave’s disease, and iodine solution to temporarily inhibit release of thyroid hormones.

**FURTHER DEVELOPMENT.** Sam is stabilized and discharged. She is very disturbed by the outcome of her noncompliance with her medication and decides to set a daily alarm on her phone to remind her to take her medication, which is now switched to methimazole, as she is well into her second trimester.

**D. Methimazole, propranolol, hydrocortisone, and iodine solution.** The doctor on call agrees that Sam will need an anti-thyroid drug. He agrees that methimazole may be used, but he would prefer to use propylthiouracil, as it may exert more rapid effects due to inhibition of de-iodination of T4. He also agrees that propranolol should be administered to counteract sympathetic overactivity.

The doctor also recommends that you also administer hydrocortisone to suppress the immune-mediated responses in Grave’s disease, and iodine solution to temporarily inhibit release of thyroid hormones.

**FURTHER DEVELOPMENT.** Sam is stabilized and discharged. She is very disturbed by the outcome of her noncompliance with her medication and decides to set a daily alarm on her phone to remind her to take her medication, which is now switched to methimazole, as she is well into her second trimester.

**E. Propranolol and hydrocortisone.** The doctor agrees that propranolol should be administered to counteract sympathetic overactivity. He also agrees that hydrocortisone may be useful to suppress the immune-mediated responses in Grave’s disease.

He recommends, however, that you also administer an antithyroid drug. Propylthiouracil is a good choice, as it may exert rapid effects due to inhibition of de-iodination of T4. Finally, he recommends that you administer iodine solution to temporarily inhibit release of thyroid hormones.

**FURTHER DEVELOPMENT.** Sam is stabilized and discharged. She is very disturbed by the outcome of her noncompliance with her medication and decides to set a daily alarm on her phone to remind her to take her medication, which is now switched to methimazole, as she is well into her second trimester.

**Part 4: Labor**

Six months later, Sam gives birth to a healthy baby girl. Sam is very happy to be a mother and is settling in well to her new role at first. Six months later, Sam is having difficulties with breastfeeding her baby. She tells the pediatrician that, at first, she was producing a lot of milk, but she now thinks that her milk production is not enough to keep her baby well fed. Sam tells the pediatrician that one of her friends was taking a drug to increase her milk supply, and she would like her to prescribe this for her. The pediatrician reluctantly agrees.

What is the mechanism of action of the drug that Sam was most likely prescribed?

- **A. Dopamine agonist.** Dopamine agonists would in fact decrease milk production. Remember that dopamine has an inhibitory effect on secretion of prolactin from the anterior pituitary.
- **Please go back and try again.**

- **B. Dopamine antagonist.** Well done! Indeed, dopamine has an inhibitory effect on secretion of prolactin from the anterior pituitary. Therefore, blockade of dopamine receptors would be expected to increase milk production.
- **C. Vasopressin analog.** Are you sure? Vasopressin analogs are not used to increase prolactin levels. They are indicated in treatment of central diabetes insipidus, persistent nocturnal enuresis, prophylaxis against bleeding in hemophilia, and initial treatment of bleeding esophageal varices.
- **Please go back and try again.**

- **D. Somatostatin analog.** Are you sure? Somatostatin may in fact exert an inhibitory effect on secretion of prolactin, which would be expected to decrease milk production. Somatostatin analogs may be used to treat acromegaly, hormone-secreting tumors and esophageal bleeding.
- **Please go back and try again.**

- **E. Somatostatin antagonist.** Are you sure? Somatostatin may exert an inhibitory effect on secretion of prolactin; therefore, blockade may indeed lead to increased prolactin release and increased milk production. However, there are no somatostatin antagonists in clinical use.
- **Please go back and try again.**

**Part 5: Methimazole Adverse Effect**

Two years later, Sam attends her endocrinologist complaining of a low-grade fever, arthralgias, and sore throat. Dr. Raj discontinues methimazole immediately. Once Sam recovers with appropriate treatment, Dr. Raj discusses her options and recommends that she undergoes treatment with radioactive iodine. Dr. Raj informs her that she will most likely need life-long thyroid replacement therapy afterwards.

Which drug would Sam be most likely prescribed for this indication?

- **A. Carbinazole.** Dr. Raj looks over to you in clear disappointment. She is not sure why you would prescribe an anti-thyroid drug for thyroid replacement therapy.
- **Please go back and reconsider.**

- **B. Iodine.** Dr. Raj is surprised that you would use iodine for thyroid replacement therapy. Do you remember that iodine is used in preparation of hyperthyroid subjects for surgical resection and as part of the treatment of severe thyrotoxic crisis?
- **Please go back and try again.**

- **C. Levothyroxine.** Dr. Raj commends you on your pharmacological knowledge. Indeed, levothyroxine is a synthetic form of T4, and it is the treatment of choice for thyroid replacement therapy.
D. Liothyronine. Dr. Raj agrees that this drug, which is a synthetic form of T3, may be used in thyroid replacement therapy. However, she advises that, due to its short half-life, cost, and route of administration, this is not the preferred treatment.

Please go back and reconsider.

E. Pegvisomant. Dr. Raj is surprised that you would recommend a growth hormone antagonist for thyroid replacement therapy. Do you remember the clinical indication for this drug?

Please go back and try again.

Part 6: Epilogue

A year later, Sam’s condition is well-controlled subsequent to radioactive iodine and thyroid replacement therapy.

While she is relieved that she is doing well, she cannot help but wonder whether her baby girl will eventually develop Grave’s disease.

Figure A2 shows the case map, with the highlighted pathway being the optimal pathway.

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No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

P.N. conceived and designed research; P.N. performed experiments; P.N. prepared figures; P.N. drafted manuscript; P.N., P.M., and S.A.N. edited and revised manuscript; P.N., P.M., and S.A.N. approved final version of manuscript.

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