

# Using Vincent van Gogh's Illnesses to Revise Medicinal Chemistry

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## ABSTRACT

**Objective:** Review sessions provide an opportunity for the students to revise materials they have learned previously. A case study has been designed using the story of Vincent van Gogh, a legendary painter with various illnesses. With this case study, almost all kinds of central nervous system drugs, including antidepressants, sedative-hypnotics, anti-epileptics, analgesics and antipsychotic drugs were reviewed, and several basic concepts of medicinal chemistry were revised, from pharmacokinetics and drug discovery to structure-property and structure-activity relationships. **Methods:** a series of student tests were performed to evaluate the effect of case study teaching. This study was designed to examine whether the method of review had any effect on three main factors: final exam performance, study habits and interest in medicinal chemistry. In total, 168 students in three classes participated in the study, 83 in the case-based review group (case study of van Gogh's illnesses) and 85 in the control group (traditional review materials). All of the students attended these classes separately and there was no significant difference in attendance. Both classes were held during normal class time, which meant that students did not need to make special accommodations in order to attend. **Results:** The students who attended this review course had positive outcomes in terms of their concluding final exam performance, study habits, and student interest in medicinal chemistry. **Conclusion:** Case study from famous people's legend story could increase the students' interest. This method could potentially be used as a new teaching method to revise medicinal chemistry.

**Key words:** Second-Year Undergraduate, Chemical Education Research, Analogies/Transfer, Medicinal Chemistry.

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## INTRODUCTION

The range of pharmaceuticals has increased rapidly with increasing economic development in our society, and consequently, the education of students regarding pharmacy has become more and more important. Medicinal chemistry is an important course in pharmacology. However, it is often difficult for students to maintain their interest and concentrate throughout their studies.

Creating excitement in the classroom through active learning, which allows students to become active participants in the learning process, is an important means for the development of a student's skills. At the

same time, it encourages the exploration of the attitudes and values that students hold.<sup>1</sup> Review sessions are a very important resource for learning course materials, as talking, writing, listening and reflecting are four elements that enable students to clarify, question and consolidate new knowledge.<sup>2</sup> Case studies are often applied in pharmacology education classroom to enhance active learning worldwide.<sup>3</sup> However, there are certain drawbacks of this method, as they can be too professional, boring, etc. Hence, the demand for means that can



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encourage a desire for learning of students and change the classroom atmosphere is on the rise.

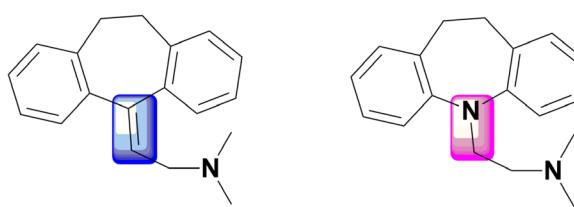
During a biography of the great artists, it was surprising to find that Vincent van Gogh, whose life was transient, but legendary, lived with various disease in addition to numerous disorders that were diagnosed after his death.<sup>4</sup> It has been reported that his illnesses resulted from disorders of the central nervous system.<sup>4,5</sup> Nowadays, central nervous system drugs, such as antidepressants, sedative-hypnotics, anti-epileptics and antipsychotic drugs, may have been used to treat these illnesses.

Thus, in this present study, we used the various afflictions of the famous artist Vincent van Gogh as a case study to aid the review of central nervous system drugs in medicinal chemistry. All of the study materials were covered in the medicinal chemistry course prior to the review session. By discussing, listening and reflecting, the central nervous system drugs were reviewed in an active-learning environment. Some basic concepts of medicinal chemistry and the general processes of drug discovery were also reviewed. This new teaching tool was found to enable the students' initiative for study and cultivate good study habits.

### Case Study: The Life of Vincent van Gogh

Vincent van Gogh (1853-1890) was a Dutch post-impressionist painter, whose work influenced 20<sup>th</sup> century art, as well as many modern-day artists. Despite his talent, from 1869 to 1886 van Gogh suffered severe depression, which was linked to amorous infatuations and failed careers.<sup>4</sup> This was indicated by his letters to his family and friends, which were related to depression.<sup>6</sup> For example, he wrote in a letter to his brother Theo, "My only anxiety is, how can I be of use in the world?" Through these letters, students were introduced to the symptoms of depression, including feelings of hopelessness or worthlessness and so on. Then, a review of various anti-depressant drugs including norepinephrine (NE) reuptake inhibitors, monoamine oxidase (MAO) inhibitors and 5-hydroxytryptamine (5-HT) reuptake inhibitors was conducted. It is worth mentioning that, when reviewing the NE reuptake inhibitors, the structural differences between imipramine and amitriptyline were made apparent (Figure 1) and, through discussion of these structures, the concept of bioisosteres in medicinal chemistry was also revised.

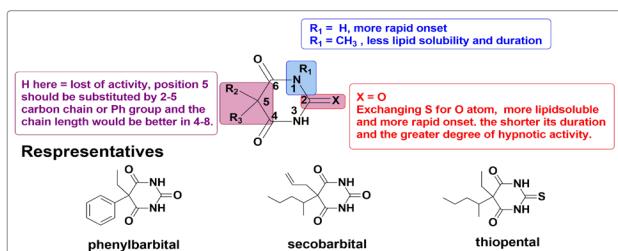
During his lifetime, van Gogh also suffered from insomnia. Another letter from van Gogh to his brother Theo read, "For three weeks I have been suffering from insomnia and low fever, and passing water was painful." Furthermore, in the letters from van Gogh to Theo



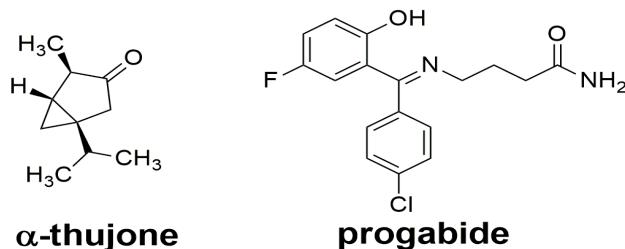
Amitriptyline

Imipramine

**Figure 1:** The structures of amitriptyline and imipramine are shown, where the blue and purple highlighted regions were bioisosteres of each other.



**Figure 2:** Structure-activity relationships of barbital derivatives and main representative of barbital derivatives.



α-thujone

progabide

**Figure 3:** Structures of the γ-aminobutyric acid (GABA) receptor antagonists, α-thujone and progabide.

and in the letters from their parents to Theo between 1878 and 1884, van Gogh's insomnia was referred to at least eight times.<sup>6</sup> Insomnia is a sleep disorder in which there is an inability to fall asleep or to stay asleep for as long as desired. Nowadays, insomnia could be treated with sedative-hypnotic drugs including phenobarbital and its derivatives. Their structure-activity relationships are shown in Figure 2. The sedative-hypnotic drugs can be divided into ultra-short-, short-, intermediate-, and long-acting types, which are divided by the metabolism of these drugs. The key points of drug metabolism, such as their phase I and phase II metabolism, were also discussed. For example, the enhancing effect of phenobarbital on cytochrome P450 enzymes and the inhibitive effect of the anti-ulcer agent cimetidine were covered. The effects of drugs on phase I and phase II metabolism can have serious consequences for patients taking warfarin (an anticoagulant drug) and other life-saving

medication and it is important for students to appreciate these effects as a part of their learning.<sup>7</sup>

Triazolam and zolpidem were also reviewed in this section and, for zolpidem, the concept of the first-pass effect was debated. After the discussion on sedative-hypnotic drugs, the students were asked their opinion on whether phenobarbital could also be used to treat seizures, as well as insomnia. The answer was “sure”, which demonstrated that the students appreciated the mechanisms of action of phenobarbital.

In 1886, van Gogh joined his brother in Paris for 2 years, where he experienced seizures that were thought to be due to his consumption of absinthe. This is an alcoholic beverage that contains  $\alpha$ -thujone, a  $\gamma$ -aminobutyric acid (GABA) receptor antagonist (Figure 3).<sup>8</sup> This led to discussion of the anti-epileptic drug progabide (Figure 3), which is a prodrug of GABA. After an enthusiastic discussion about the relationship between seizures and GABA receptor antagonists or agonists, some basic concepts of medicinal chemistry were re-examined, such as agonists and antagonists, prodrugs etc. Other anti-epileptic drugs, such as phenytoin sodium and carbamazepine, were also discussed.

In the fall of 1888, van Gogh and Eugène Henri Paul Gauguin, a French post-impressionist artist, establish together a “Studio of the South”. However, the relationship between the two artists ended catastrophically. On 23<sup>rd</sup> December 1888, Gauguin left the studio and van Gogh cut off part of his left earlobe with a razor. This led to a review of analgesics, such as morphine, pethidine and pentazocine etc. Morphine analogues were also discussed, including codeine, heroin and naloxone, amongst others. By examining the structures of the typical analgesic drugs, students were able to identify the SAR of morphine analogs more easily.

It is interesting to note the striking use of a yellow corona around each star in van Gogh's famous painting “The Starry Night”. Van Gogh's use of the yellow pigment may have been influenced by digitalis therapy which, at the time, was thought to control seizures.<sup>9</sup> In one of van Gogh's three portraits of his physician Paul-Ferdinand Gachet, the subject holds a stem of *Digitalis purpurea* (purple foxglove) from which the drug digitalis is extracted. Recently, huperzine A, which is a naturally occurring alkaloid found in the firmoss *Huperziasterrata*, was assessed for its efficacy at preventing seizures in rodents.<sup>10</sup> From here, lead compounds extracted from natural products were discussed with the students, as well as other sources of potential lead compounds. The general processes of drug discovery were then introduced to the college students.



**Figure 4: The artwork that incorporated the structure of morphine in the style of van Gogh.**

Plagued by psychiatric illness throughout his life, van Gogh is thought to have committed suicide in 1890. This permitted a review of antipsychotic drugs. The structures of chlorpromazine and chlorprothixene were used as a comparison. The antipsychotic effect of chlorprothixene resides mainly with the *cis* isomer, while the *trans* isomer is less active, thus the *trans* isomer is considered as an impurity. From the example of chlorprothixene, the concept of configurational isomers having different chemical and physical properties was introduced to the students. This idea was then expanded into a discussion of structure–property relationships (SPRs) and their importance in medicinal chemistry.<sup>11</sup> Finally, an artwork that included a structure of morphine in the style of van Gogh was used to complete the review course in a relaxed atmosphere (Figure 4).

## Results and Discussion

Many myths, theories and diseases have surrounded famous artistic painters, composers and philosophers throughout the years.<sup>12</sup> Using these as case studies in the education of medicinal chemistry could be better than some of the traditional case studies.

In this present study, through appreciation of the conditions suffered by Vincent van Gogh, central nervous system drugs were reviewed with college-level students. The reviewed drugs included antidepressants, sedative-hypnotics, anti-epileptics, analgesics and antipsychotics. Some basic concepts of medicinal chemistry were covered, such as pharmacokinetics and drug discovery, as well as SPRs and SARs. Furthermore, the general processes of drug discovery were introduced to the college students.

As a successful case study depends on how effectively it facilitates the acquisition, integration and application of information and how engaging it is to the students. Thus, a series of student tests were performed to evaluate the effect of case study teaching. This study was designed to examine whether the method of review had any effect on three main factors: final exam performance, study habits and interest in medicinal chemistry. In total, 168 students in three classes participated in the

**Table 1: The outcomes of the investigation according to the questionnaire completed by the students.<sup>a</sup>**

Parameters compared	Student responses (n = 168)	
	Case-based review n = 83	Traditional review n = 85
Attended final review session (%)	100	100
The accuracy of multiple choice exercise in the final exam (%)	86.60 ± 5.80 <sup>*c</sup>	67.03 ± 0.51
Interest in medicinal chemistry before review <sup>b</sup>	2.42 ± 0.58	2.83 ± 0.67
Interest in medicinal chemistry after review <sup>b</sup>	8.54 ± 1.24 <sup>**c</sup>	3.21 ± 1.62

<sup>a</sup>The results were expressed as mean ± SD;<sup>b</sup>A 10-point scale was used, with 10 being the highest possible score;<sup>c</sup>\*p < 0.05, \*\*p < 0.01 compared with the traditional review group.

study, 83 in the case-based review group (case study of van Gogh's illnesses) and 85 in the control group (traditional review materials). All of the students attended these classes separately and there was no significant difference in attendance (Table 1). Both classes were held during normal class time, which meant that students did not need to make special accommodations in order to attend.

Firstly, the performance of students in the case-based review and traditional-based review classes were markedly different. From a qualitative point of view, the class atmosphere was more active and excited in the van Gogh case-based review and the students were able to concentrate throughout the class. In the final exam, the accuracy of the multiple choice exercises related to the review contents for the 83 students in the van Gogh group was 86.60% ± 5.80% compared to 67.03% ± 0.51% for the 85 students in the traditional review group. There was a marginally significant difference ( $p = 0.041$ ) between the case-based review and traditional review groups. Finally, the outcomes from this course were positive and student evaluations indicated that more than 66% of college students strongly agreed that learned a lot in the van Gogh case-based class. Students also agreed that discovering the importance of medicinal chemistry through van Gogh's illnesses was more interesting than through a traditional review. The students' interests in medicinal chemistry were assessed before and after the case study review on a scale from 1 to 10 (10 = very interested, 1 = not at all interested). The average level of student interest in medicinal chemistry before the review session was 2.42 ± 0.58 in the case-based review group and 2.83 ± 0.67 in the control group. The feedback from students was generally favorable. The students in the case-based group (54%) had an increased average level of interest in subject after the review session to 8.54 ± 1.24, more than the 3.21 ± 1.62 reported by the traditional review group students. It was worth mentioning that the students

who attended the case review of van Gogh had also attended the traditional review previously. This new teaching approach could enhance the willingness of students to study this subject and the cultivation of good study habits.

## CONCLUSION

In this present study, we described the legendary life and illnesses of Vincent van Gogh, and a range of related central nervous system drugs. This teaching approach enables students to study in an exciting and active atmosphere. After the review session, most of the students reflected that they had learned a lot in the class and had become more aware of the importance of medicinal chemistry. Most importantly, the current results suggest that there was a marked increase in the interest of students in the field of medicinal chemistry after being taught this case study.

However, we should point out that a minority of students only remembered the story of Vincent van Gogh, and did not acquire the appropriate knowledge about central nervous system drugs. Efforts will be made to improve this finding in future versions of this case-based teaching approach.

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## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

## ABBREVIATIONS USED

**NE:** Norepinephrine; **MAO:** Monoamine oxidase; **5-HT:** 5-hydroxytryptamine; **GABA:**  $\gamma$ -aminobutyric

acid; **SPRs:** Structure-property relationships; **SARs:** Strcture-activity relationships.

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## SUMMARY

- A case study has been designed using the story of Vincent van Gogh, a legendary painter with various illnesses.
- With this case study, almost all kinds of central nervous system drugs were reviewed and several basic concepts of medicinal chemistry were revised.
- The students who attended this review course had positive outcomes in terms of their concluding final exam performance, study habits, and student interest in medicinal chemistry.

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