

BUPROPION OVERDOSE



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Union dead, scattered at the base of Little Round Top, battle of Gettysburg, 2nd July 1863, (T.H O'Sullivan)

...Through the night the two armies continued to gather. After a 35 mile all night march, Union general John Sedgwick arrived with his 6th corps. By morning 65,000 Confederates faced 85,000 Federal troops commanded by General George Meade. Hills overlooked the federal positions at either end - to the north, on the Union right, Culp's Hill and Cemetery Hill, to the south, the Big and Little Round Tops Lee wanted then taken. Meade was no less determined to hold his ground. "All commanders are

authorized to order the instant death of any soldier who fails in his duty at this hour". It took Longstreet all morning and afternoon to shift two divisions into position for the assault on the Round Tops. Assigned to hold the Union position was General Dan Sickles, a turbulent ex-tammany hall politician best known before the war for having shot and killed his wife's lover. Now Sickles disobeyed orders and marched his men further out from Little Round Top to the Devil's Den, the Wheat Field, and into the Peach Orchard beyond. He was half a mile in front of the Union line on a flat, exposed position that left the Round Tops completely undefended.

The rest of the army was amazed. Someone said he stuck out like a sore thumb. And I think it was Hancock who saw him go out, and he said. "Wait awhile, you'll see him tumbling back" and of course he did. (Shelby Foote Civil War Historian)

The Confederates finally attacked at 4 o'clock in the afternoon. As they swept forward the 15th Alabama regiment scrambled up Big Round Top. From there well above the fighting Colonel William C. Oates saw his chance. Little Round Top was completely undefended. From that position, Oates said, he could blow the whole Union army apart. "Within half an hour, I could convert Little Round Top into a Gibraltar that I could hold against 10 times the number of men that I had". Meanwhile, Meade dispatched General G.K Warren to the summit. He immediately saw the danger. Only a handful of signal men held the hill. Oates' Confederates were moving down and around the Union left. Warren sent at once for reinforcements. Four Union regiments raced up Little Round Top

"In a moment all was excitement. Every soldier seemed to understand the situation and to be inspired by its danger. Away we went under the terrible artillery fire. Shells were exploding on every side. But our men appeared to be as cool and deliberate in their movements as if they had been forming a line upon the parade ground in camp. Up the steep hillside we ran and reached the crest"

At the extreme left of the Union line now was Joshua Lawrence Chamberlain's 20th Maine. Oates's Alabamians were already moving between the two hills. Chamberlain's orders were to "Hold that ground at all costs".

"Imagine if you can, none small companies of infantry numbering perhaps 300 men in the form of a right angle. On the extreme flank of an army of 80,000 men put there to hold the key of the entire position against a force at least 10 times their number". (Union soldier)

"Stand firm you boys from Maine, for not once in a century are men permitted to bear such responsibilities for freedom and justice for God and humanity, as are now placed upon you".

360 Maine men now took cover behind boulders. They had less than 10 minutes to spare. At the last possible moment, Chamberlain sent his company B across the hollow between the hills to bolster his left flank. Before they were in place, Oates' Confederates charged up the slope. Chamberlain assumed company B had been wiped out. He could not afford the loss. The Maine men opened fire into the charging rebels. Oates' men staggered but regrouped and came at them again.

“The line had broken because of the timber and the first fire of the hidden Federals. A long line of us went down, three of us close together. There was sharp electric pain in the lower body, and then a sinking sensation to the earth, and falling, all things growing dark, the one and last idea passing through the mind was, this is the last of earth”
(Private W.C Ward, 4th Alabama, wounded at Little Round Top)

“The enemy was pouring a terrible fire upon us, his superior forces giving him a great advantage. The air seemed to be alive with lead. The lines at times were so near each other the hostile gun barrels almost touched” (Union soldier)

The Southerners drove the Maine men from their positions five times. Five times they fought their way back again. Saplings were gnawed in two by bullets.

“At times I saw around me more of the enemy than of my own men - gaps opening, swallowing, closing again - squads of stalwart men who had cut their way through us disappearing as if translated. All around, a strange, mingled roar”.

In an hour and a half one third of Chamberlain’s men fell. Sounds of battle now increased behind the 20th Maine, Chamberlain assumed Little Round Top was being surrounded.

“Our ammunition is nearly all gone and we are using the cartridges from the boxes of our wounded comrades. A critical moment has arrived and we can remain as we are no longer. We must advance or retreat. It must not be the latter, but how can it be the former”? (Union soldier)

Chamberlain’s only choice was to attack, and now he conjured up an unlikely textbook maneuver. With his men almost out of ammunition, he ordered them to fix bayonets. Then, while the right of his line held straight, he had his left plunge down the hillside all the while wheeling to the right - “Like a great gate upon a post” an eye witness said. The Confederates were taken completely by surprise. Those in the front ranks dropped their weapons. Those behind turned and ran.

“Many of the enemy’s first line threw down their arms and surrendered. An officer fired his pistol at my head with one hand while he handed me his sword with the other”.
(Union soldier)

The Confederates had gone only a few paces when from their left came a second horrifying surprise. Chamberlain’s missing company B, which had found protection behind a stone wall, now rose and fired.

“While one man was shot in the face, his right hand comrade was shot in the side or back. Some were struck simultaneously from two or three balls from different directions”.
(Colonel William C. Oates) Oates’ men wavered, broke, and ran for their lives. “My dead and wounded were then nearly as great in number as those still on duty, they literally covered the ground. The blood stood in puddles in some places on the rocks. The ground was oaked with blood”

Joshua Lawrence Chamberlain's scanty force captured 400 Confederates. Little Round Top held..... But far out in front of the Union lines, General Sickles and his men were in desperate trouble. The rebels were closing in from three sides. Confederate shells tore branches from the peach trees and bounded among the men.

"The hoarse and indistinguishable orders of commanding officers, the screaming and bursting of shells, canister, and shrapnel as they tore through the struggling masses of humanity, the death screams of wounded animals, the groans of their human companions, wounded and dying and trampling underfoot by hurrying batteries riderless horses and the moving lines of battle. A perfect hell on Earth, never perhaps to be equaled, certainly not to be surpassed nor ever to be forgotten in a man's lifetime. It has never been effaced from my memory, day or night, for 50 years"

(Private Robert H. Carter, 22nd Massachusetts)

"The balls were whizzing so thick", a Texan remembered, "that it looked like a man could hold out a hat and catch it full".

"I was within a few feet of General Sickles when he received the wound by which he lost his leg. A terrific explosion seemed to shake the very earth, instantly followed by another. I noticed that his pants and draws at the knee were torn clear off to the leg, which was swinging loose. He was carried from the field, coolly smoking a cigar". (Union soldier)

Sickles' men counterattacked, fell back, held, pushed the Confederates back, then retreated again through places still remembered for the ferocity of the fighting that happened there - the Wheat Field - The Slaughter Pen - Devil's Den - the Valley of Death. Finally the fighting subsided. Of the 262 in one Minnesota regiment, only 47 survived unhurt. 82% had fallen in less than 5 minutes. No Union regiment in the war suffered greater casualties. Company F of the 6th North Carolina lost 100 %.

"Dear Father, finally I came to poor Albert lying on the ground, wounded under the left eye. He had also had a ball shot through his left leg. I had no one to help me bear him from the field. I then called a captain of another company to assist me and we bore Albert 600 yards through a dense swamp, all bleeding and sore with pain, before we could find any of the ambulance corps to bear him off to the hospital. Taking him in my arms, I assisted him in the stretcher, dropping a tear of grief upon his bleeding face, I bade him goodbye"

(Charles Batchelor)....

"Who was victorious or with whom the advantage rests no one here can tell. Some think the rebels were defeated as there has been no boasting as on yesterday and they look uneasy and by no means exultant. I fear we are too hopeful. We shall see tomorrow (Sallie Broadhead, Gettysburg resident)

"As the Sun set, the Union left and right still held. Lee was sure an all-out Confederate attack on the center the next day would work. "When the second day's battle was over, General Lee pronounced it a success, but we had accomplished little towards victorious results" (Confederate General James Longstreet).

The first day's fighting was so encouraging, and the second day's fighting came within an inch of doing it. And by that time Longstreet said Lee's blood was up. And Longstreet said when his blood was up, there was no stopping him. Longstreet tried to stop him and Lee said, "No, he's there", meaning the enemy, "and I'm going to strike him" (Shelby Foote, Civil War Historian)

General Longstreet, I think had good reason to worry about attacking the Union position at Gettysburg. After all, it was his corps at Fredericksburg that mowed down the Union troops in front of the stone wall. He could realize what the rifled musket could do held in the hands of determined troops. (Ed Bearss, Civil War Historian)

The next day was Pickett's charge...

David McCullough and Shelby Foote in Ken Burns', "The Civil War", 1990.

When a patient presents with bupropion overdose, every staff member must immediately understand the strategic situation! Though the potential for disaster is high, all staff must remain cool and deliberate in their movements as if forming a line upon the parade ground in camp!



Big and Little Round Tops, outside of Gettysburg, c. 1863.

BUPROPION OVERDOSE

Introduction

Bupropion (trade name in Australia “**Zyban**”) is **monocyclic antidepressant** agent.

It is used as such in North American, however in Australia it is solely used to specifically **suppress nicotine craving**.

The mechanism by which it does this is unknown.

In Australia it is only available as an **extended release** preparation.

There is a high risk of seizures in overdose of any amount and the potential for lethal cardiotoxicity in very high overdose.

Management consists of benzodiazepine sedation and supportive care.

History

Bupropion was developed by Indian-born American organic chemist and pharmacologist **Nariman Mehta** of Burroughs-Wellcome (now Glaxo-Smith-Kline) in 1969.

It was approved by the United States FDA for use as an antidepressant in 1985.

It was withdrawn the following year because of a high incidence of seizures. The risk of seizure was found to be highly dose dependent, and so it was reintroduced in 1989 with a lower maximum recommended daily dose

In 1996, the FDA approved a sustained-release formulation.

In 1997 it was approved by the FDA for use as a smoking cessation aid under the trade name of “Zyban”

In 2012, the U.S. Justice Department announced that GlaxoSmithKline had agreed to plead guilty and pay a 3 billion USD fine, in part for promoting the unapproved use of bupropion for weight loss and sexual dysfunction

Preparations

Bupropion extended release as:

Tablets:

- 150 mg.

Toxicology

Bupropion is a monocyclic antidepressant agent that is able to suppress nicotine craving by an unknown mechanism.

It acts centrally to inhibit the re-uptake of **noradrenaline**, **dopamine** and to a lesser extent **serotonin**.

It also has some anticholinergic effects.

Pharmacokinetics

Absorption:

- Bupropion is well absorbed orally with peak levels occurring within 2-3 hours.

Distribution:

- It has a large volume of distribution at 19.8-47 litres/ kg

Metabolism and excretion:

- Bupropion is metabolized in the liver to active metabolites, which are renally excreted.

Risk Assessment

There is a high risk of seizures following overdose of **any amount**.

First seizure is usually within **2-8 hours**, but may be delayed up to **24 hours**.

The risk of seizures is greater in those with:

- Seizure disorders
- Co-ingestion of other **proconvulsant** drugs such as centrally acting sympathomimetic or serotonergic agents.

Dose related risk assessment:

Dose	Clinical effects
Any dose	Seizures Tremor/ agitation

	<p>Tachycardia/ hypertension</p> <p>Agitation/ confusion/ hallucinations</p> <p>GIT upset</p>
> 4.5 grams	50% risk of seizures, usually within 8 hours of ingestion.
> 9 grams	<p>Very high risk/ universal of seizures</p> <p>ECG abnormalities; prolonged QRS / QT</p> <p>Ventricular arrhythmias.</p> <p>Death</p>

Clinical Features

Clinical features develop progressively over a period of 6-8 hours.

1. Initial symptoms include:

- GIT upset
- Tachycardia/ hypertension.
- CNS:
 - ♥ Tremor.
 - ♥ Altered mental state/ agitation/ hallucinations.

In more severe toxicity the following may then occur:

2. Seizures:

- Usually occur within 8 hours, however they may be delayed beyond this time, up to 24 hours in the case of slow release preparations .

3. Cardiac toxicity may occur following large ingestions, (i.e. > 9 grams):

Features include:

- Tachyarrhythmias
- Widened QRS / QT complex.
- Hypotension.

Investigations

1. U&Es/ glucose.
2. Consider the possibility of coingestion, paracetamol and blood alcohol levels.
3. ECG:
 - Baseline 12 lead ECG and then at **6 hours** and **12 hours** post ingestion.
 - Prolonged **QT** and **QRS**
 - If ingested amount is **> 4.5 grams** the ECG should be repeated **2 hourly** or sooner if symptoms develop.

Management

1. Immediate attention to any ABC issues:
 - IV access in all cases.
 - The threshold for intubation should be low
Patients should be intubated if they have ingested **> 9 grams**
2. Charcoal:
 - This should be **avoided** because of the **high risk of seizures**.
 - It may be given via nasogastric tube *following* intubation.
3. Whole bowel irrigation:
 - Current expert opinion states that this should *not* be done due to the high risk of seizures.
4. Agitation/ confusion tachycardia
 - Give titrated IV doses of diazepam.
Early use of IV diazepam will reduce the risk of subsequent seizures.

Give 2.5 - 5.0 mg IV, every 2-5 minutes until mild - moderate sedation and pulse rate < 100 is achieved.

5. Seizures:

- These should be treated aggressively with IV diazepam.

6. Tachyarrhythmias and widening of the QRS:

- Broad complex tachyarrhythmias **should be treated with IV sodium bicarbonate.**

Give 1 - 2 mmol/kg IV every 1 - 2 minutes to achieve alkalization as for sodium channel toxicity in general

Disposition:

Patients should be observed for a **minimum of 24 hours** if they have ingested **> 4.5 grams**.

Those who are symptom free and with a normal ECG after this time period may be medically cleared.

References

1. Bupropion in L Murray et al. Toxicology Handbook 3rd ed 2015.
2. Balit CR, Lynch CN, Isbister GK. Bupropion poisoning: a case series. Med J Aust 2003;178 (2): 61- 3.
3. eTG - July 2017.

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