Stimulation of the Internal Globus Pallidus and the Subthalamic Nucleus for Parkinson’s Disease

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Deep brain stimulation of the internal globus pallidus (Gpi) or the subthalamic nucleus (STN) effectively reduces parkinsonian motor symptoms and alleviates motor fluctuations. Parkinsonian patients in good general health, who are neither depressive nor demented and are severely disabled despite all available medication strategies, are potential candidates for this therapy. Typically, a good response to a suprathreshold dose of levodopa preoperatively is indicative of good results with deep brain stimulation. This therapy may be applied bilaterally without resulting in some of the permanent side effects of bilateral lesions.

Programming deep brain stimulation is a lengthy procedure and requires expertise in the management of movement disorders. This monograph describes the initial programming process and subsequent adjustments, and addresses considerations before discharging the patient. The last section provides specific product-related recommendations for programming the Kineta™ neurostimulator.
A neurologist, with expertise in movement disorders and experience in using motor rating scales for Parkinson’s disease, i.e., the Unified Parkinson’s Disease Rating Scale (UPDRS), should perform initial programming. Before initiating the programming process, the neurostimulator(s) should be internalized. In rare cases, where no clear physiological responses have been achieved intraoperatively, using temporary, external stimulation might be considered.

Because initial programming involves the cooperation of the patient, it should not be performed immediately after the patient’s return from the operating room. Usually initial programming begins the day after the implantation of the neurostimulator. The patient must be in a stable OFF medication state and be alert and coherent enough to cooperate during programming.

In some patients, however, their clinical condition may be improved in stimulation OFF immediately postoperative due to healing, peri-subthalamic edema or the surgery-related effects of micro-pallidotomy and micro-subthalamotomy. This could delay the timing of initial programming.

If the patient’s condition allows it, the patient should be OFF antiparkinsonian medication to induce a “worst off” condition. In some patients, however, it may be difficult to perform initial programming in a “worst off” condition so shortly after a long and tiring surgery. Some “off” state conditions, such as “off” phase dystonia, may also be painful, making the evaluation of the patient difficult. In these cases, a moderate “off” state with some medication is more desirable. If GPi stimulation is prescribed primarily for L-dopa-induced dyskinesias, it is essential to perform the adjustment under “best on” conditions where medication-induced dyskinesias are present.

**Objective**
- To test the impedance and current drain of each of the four electrodes for each lead.

Impedance and current drain measurements help to identify causes of inadequate or no stimulation effects. These are usually tested during the first programming session and can also be helpful for troubleshooting whenever a patient’s motor state worsens or positive effects do not occur. Measuring impedance regularly during subsequent programming sessions is also recommended.

**Method**
- Test each electrode individually in unipolar mode by selecting the IPG OUTPUT function, and then the IMP function. This measurement permits long-term comparison of impedance readings for a single patient. Adjust the neurostimulator in continuous mode, using the standard setting for maximum accuracy in impedance measurement as follows:
  
  - Amplitude = 1.0 V
  - Rate = 30 Hz
  - Pulse Width = 210 µs.
1. INITIAL PROGRAMMING

Unipolar stimulation:
One or more of the four electrodes of the DBS™ lead serves as the negative pole (cathode) and the neurostimulator case functions as the positive pole (anode). Typically only one electrode is activated.

Bipolar stimulation:
One or more electrodes of the DBS lead serves as the positive pole (anode), and one or more of the remaining electrodes functions as the negative pole (cathode). The typical bipolar setting consists of one positive and one negative electrode.

• Program one of the electrodes “0”; “1”; “2”; or “3” to be the negative pole and the neurostimulator case to be the positive pole.

Note: Impedance close to 2000 Ohms can only be measured accurately at relatively high amplitudes or pulse widths. However, it is possible to use the therapeutic stimulation parameters for impedance measurements if the impedance is within a lower range.

Troubleshooting
• The implantable pulse generator (IPG) does not reliably measure impedance greater than 2000 Ohms, and a current drain lower than 7 \( \mu \)A indicates that no current is flowing in the tested electrode. To investigate a possible problem, repeat the measurement with two or more active electrodes in a unipolar setting. Theoretically, the impedance should be reduced by approximately half when activating two electrodes or to approximately a third when activating three electrodes. Concomitantly, the current drain should be doubled when using two electrodes, and tripled when using three electrodes.

• If the impedance remains higher than 2000 Ohms with two or more active electrodes, a break in the neurostimulator-connector-lead circuit or a connection problem probably exists.

• If an impedance problem is detected only in one electrode, it should not be used for programming.

• If the impedance problem is found in more than one electrode, a radiograph of the Activa® System may assist in detecting possibly larger breaks.

• If the impedance is very low (< 50 Ohms) and the current drain is high (> 2000 \( \mu \)A), a short-circuit may be suspected. This may be due to a break in the insulating material, which can cause the patient to experience a subcutaneous burning sensation at the location of the short circuit.

• After a few hours, repeat impedance measurements for each electrode with an impedance greater than 2000 Ohms to reproduce and confirm the results.
Objective

- To evaluate the efficacy of stimulation on parkinsonian symptoms at each of the four electrodes.
- To determine the threshold voltage for the onset of undesired effects for each of the four electrodes.

Method

- Set the pulse width and rate. Average parameters are: 60 µs and 130 Hz.
- Test the four electrodes of each lead individually in unipolar mode: Set the active electrode to be the negative pole and the neurostimulator case to be the positive pole.
- Make baseline measurements of tremor and rigidity, using UPDRS motor scores. Tremor and rigidity respond quickly to stimulation and are thus efficient target symptoms for initial programming.
- Evaluate the effect of stimulation of a given electrode after gradually increasing the voltage in steps of 0.5 V. Each voltage level should be applied for 30 to 60 seconds unless unacceptable stimulation-induced side effects occur immediately.
- Assess parkinsonian symptoms quantitatively at every 0.5 V to 1 V increment after applying stimulation for 30 to 60 seconds. Apply increments of 0.5 V or even 0.2 V if 1 V increments become too great.
- The maximum voltage the patient can tolerate should be applied for a few hours and the effects on parkinsonian symptoms should be re-evaluated in medication-ON condition.
- Record each threshold that induces transient and permanent stimulation-induced side effects. Most stimulation-induced side effects occur transiently first and then become permanent. However, there may be exceptions, e.g., permanent motor contractions are usually preceded by transient paresthesia.

Note: It is desirable to establish a wide therapeutic window between stimulation benefits and stimulation-induced side effects. Therefore, the electrode with the lowest threshold for antiparkinsonian effects and the highest threshold for side effects is selected for long-term stimulation. The voltage must not be increased beyond the threshold of permanent side effects.

Generally, transient undesirable effects such as motor contractions appear at a lower threshold if the voltage is increased slowly and gradually. Any stimulation-induced side effect can occur fleetingly at low voltage and then permanently at a higher voltage. The occurrence of such transient effects indicates that the threshold for side effects is imminent. Use a finer resolution of increments to find the exact threshold of the side effect.

Principal side effects observed with GPI stimulation:

- Motor contractions, due to stimulation diffusion to the corticospinal fibers, which may occur during stimulation with any of the four electrodes.
• Visual flashes, due to the proximity to the optic tract, more often observed with ventral electrodes (electrodes “0” or “1”).
• Abnormal involuntary movements, often during stimulation with the most dorsal electrodes when the electrodes are located outside of the GPi. (These side effects are not observed when all electrodes are located in the GPi.)
• Autonomic function disorders, such as nausea (ventral electrodes).
• Feelings of malaise or strangeness.
• Dysarthria or hypophonia, often appearing at the same time as motor contractions.
• Paresthesia.

Principal side effects observed with STN stimulation:

• Motor contractions, due to stimulation diffusion to the corticospinal fibers; sometimes this effect develops gradually after several hours of stimulation.
• Dysarthria or isolated hypophonia, due to stimulation diffusion to the corticobulbar fibers.
• Paresthesia, due to stimulation diffusion to the corticospinal fibers and to the medial lemniscus.
• Oculomotor function disturbances, due to electrode placement proximal to the nuclei of the oculomotor nerve.
• Equilibrium disturbances, due to electrode placement proximal to the red nucleus.
• Abnormal involuntary movements, the onset of which are usually viewed as positive because they generally indicate proper lead placement. These abnormal movements may appear several hours after stimulation; therefore, avoid making adjustments at the end of the day. In practice, abnormal movements can be avoided by keeping stimulation below the threshold.

Note: If the increase in voltage is limited by the onset of side effects, particularly dyskinesias, it may be useful to change to the bipolar stimulation mode. In this mode, the most effective electrode should be the cathode (negative pole) and an adjacent electrode should be the anode (positive pole).

Based on our experience, the following average parameters are used.

<table>
<thead>
<tr>
<th>Deep brain stimulation parameters</th>
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<tbody>
<tr>
<td><strong>Mode:</strong> continuous</td>
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<tr>
<td><strong>Electrical Configuration:</strong> unipolar or bipolar. Unipolar stimulation is typically recommended. For situations where bipolar stimulation should be used, see below.</td>
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<tr>
<td><strong>Active Electrode:</strong> choice of four electrodes, numbered from “0” to “3.” The most distal to “3” is the most proximal electrode.</td>
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<tr>
<td><strong>Amplitude:</strong> average parameters, STN = 3 V and GPi = 3.6 V</td>
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<tr>
<td><strong>Rate:</strong> average parameters, STN and GPi = 130 Hz to 185 Hz but at least 100 Hz</td>
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<tr>
<td><strong>Pulse Width:</strong> average parameters, STN = 60 µs and GPi = 60 to 90 µs</td>
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2. SUBSEQUENT ADJUSTMENTS

Objective

• To adjust amplitude and medications.

Method

Amplitude:

• Apply a relatively low voltage (about 1 V) to the electrode that was selected during initial programming. Over the course of several days, progressively increase the voltage in small increments of 0.2 V or 0.5 V, depending on the clinical efficacy and the side effects induced by stimulation.

  Note: To preserve battery life, select the minimum voltage demonstrating clinical efficacy.

• Focus primarily on akinesia when adjusting stimulation. Akinesia tends to respond more slowly to stimulation than rigidity and tremor.

Medication:

• Decrease or discontinue dopamine agonist treatment preoperatively, as necessary, to avoid immediate peri- or post-operative confusion. If needed, L-dopa may be supplemented.

• Adjust antiparkinsonian medications postoperatively, while optimizing stimulation, according to the antiparkinsonian effect of the stimulation.
  – The patient’s motor improvement from STN stimulation allows a progressive decrease in the daily dose of L-dopa. Retaining a moderate dose of antiparkinsonian medication might reduce the risk of these patients becoming apathetic after surgery.
  – Patients with STN stimulation need to be carefully watched for the onset of side effects, especially dyskinesias, after resuming medication treatment.
  – GPi stimulation dramatically decreases L-dopa-induced dyskinesias, but its effects on rigidity, tremor, and bradykinesia may be more variable and may require the patient to continue the same dose of antiparkinsonian medications as before surgery.

Objective

• To adjust other stimulation parameters.

Method

• Pulse width: Increasing the pulse width, particularly during stimulation of the GPi, improves the effect of stimulation, though to a lesser extent than an increase in voltage.

  Note: Above 3.6 V, battery current consumption in the Itrel® II neurostimulator increases considerably. For patients where a voltage higher than 3.6 V would enhance therapeutic effects, increase the pulse width to 90 µs or 120 µs. Maintain the voltage at or below 3.6 V.

• Rate: Increasing the rate above 130 Hz to 160 Hz or 185 Hz may have a favorable effect on tremor.
Objective
- To adjust and finalize programming settings.
- To program magnet amplitude for patients with an Itrel II neurostimulator.

Method
- The control magnet permits patients to activate or deactivate the neurostimulator. When programming the Itrel II neurostimulator for patients who do not require two different settings (normal and low), set the neurostimulator to low magnet amplitude (MAG–AMP) by applying the front end of the magnet to the neurostimulator for six to eight seconds. Set the physician programmer to SPECIAL, then MAG–AMP, and adjust the voltage to the same level as is used in the normal mode. The voltage is then displayed underlined. The adjustment allows uninterrupted therapy and avoids confusion for patients who inadvertently switch between normal and low magnet amplitude mode while attempting to activate or deactivate the neurostimulator.

- The SoftStart/Stop Mode feature allows stimulation to begin and end with a graduated increase or decrease in amplitude to prevent the sensation of a sudden burst of stimulation when the neurostimulator turns on normally. Use the SoftStart/Stop Mode particularly when the therapeutic window between stimulation benefit and adverse effect is narrow. Due to potential charge imbalance conditions, the SoftStart/Stop feature use should be monitored to ensure the number of activations remains within the safe zone.

- Reset the magnet activation counters to zero at each visit so that the effective stimulation time and the number of magnet activations can be monitored. Select the OUTPUT function and the USE function.

- Print the final parameters and impedance values and include them with the patient’s records. It may be useful to give the patient a copy, especially if he or she lives far from the programming clinic.

Objective
- To teach the patients how to turn their neurostimulator ON and OFF and to determine whether it is functioning.
- To educate patients about avoiding exposure to external magnetic fields and inadvertently deactivating the neurostimulator.

Method
Patients must be able to correctly apply the magnet for at least 2 seconds to the neurostimulator, and to test the neurostimulator’s operating status using a radio receiver.
A small, portable AM radio receiver may be used to ensure that the neurostimulator is functioning correctly by holding the receiver over the patient’s body (set to AM mode, approximately 530 kHz, but not to a radio station) and moving it along the path of the extension. A buzzing sound indicates that the neurostimulator is ON. Different stimulation frequencies for the two neurostimulators will result in two distinct and distinguishable buzzing sounds. This is helpful for the patients to identify whether both neurostimulators are ON.

Radio receivers with speakers should not be applied directly to the region where the neurostimulator is implanted, because some radio speakers have magnets strong enough to turn the neurostimulator OFF. If interference from speaker magnets is suspected, use a portable radio with headphones and no speakers.

Note: The sound emitted by the neurostimulator in bipolar mode is inaudible at a relatively low voltage (< 2.5 V).

Instruct patients to avoid disabling the neurostimulator through inadvertent exposure to equipment that contains strong magnets or emits electromagnetic waves, e.g., airport metal detectors, electric drilling machines, electric motors, refrigerator doors, or by an inadvertent activation by the Medtronic 7452 magnet provided to the patient.

Teach patients and their family members how to operate the neurostimulator using ON and OFF with the Medtronic 7452 magnet.
4. SPECIAL FEATURES OF THE KINETRA NEUROSTIMULATOR

Technical characteristics

- A single neurostimulator with two channels, one for each lead: channel 1 corresponds to one lead with electrodes numbered from “0” (distal) to “3” (proximal); channel 2 corresponds to the second lead with electrodes numbered from “4” (distal) to “7” (proximal).
- The impedance is measured with stimulation ON, using continuous stimulation parameters for the active electrode.
- The continuous stimulation parameters are the same as those used for the Itrel II. It is possible, however, to use a fine resolution mode (0.05 V) for the voltage when the therapeutic window is narrow. The maximum voltage available is 6.35 V when using fine resolution.
- The rate may be increased up to 250 Hz, but no study is available yet that demonstrates the need for frequencies higher than 185 Hz.

Programming

- The principles guiding the adjustment of the stimulation parameters for the Kinetra neurostimulator are the same as for the Itrel II neurostimulator.
- The voltage may be dropped to 0 V before electrodes are changed (e.g., switching from electrode “1” to “2”); however, the neurostimulator automatically reverts back to 0 V when electrodes are switched.
- The patient may use either a magnet or the Medtronic Access™ Therapy Controller to turn stimulation ON or OFF. The Access Therapy Controller also allows the patient to check if stimulation is ON or OFF. If patients use the Access Therapy Controller to prevent the neurostimulator from being deactivated accidentally by electromagnetic interference, the magnet switch in the neurostimulator needs to be disabled. If the patient uses the magnet only, the magnet switch must be activated.
- The Access Therapy Controller allows the patient personally to adjust the amplitude, the pulse width, or the rate within a range programmed by the physician. The range should be set depending on the thresholds for improvement of motor symptoms and side effects. Only the amplitude adjustment within custom limits has been used in our group. It allows the patient to adjust the amplitude within physician set limits.
- The programmed upper limit of the amplitude must be below the threshold values that induce side effects.
- The Access Therapy controller may be recommended to patients who live far from the management center, and to patients who receive beneficial effect at a low stimulation threshold in the immediate postoperative period because the threshold is likely to rise over time.
- At each programming session, the battery capacity of the neurostimulator should be measured by selecting the IPG BATT function, and then BATTERY CAPACITY. The battery voltage and an approximate percentage of the battery capacity consumed are indicated.
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References

