Movement Disorders
CLINICAL PRACTICE
REVIEW

Challenges in PD Patient Management After DBS: A Pragmatic Review

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Abstract: **Background:** Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or internal globus pallidus (GPi) represents an effective and universally applied therapy for Parkinson's disease (PD) motor complications. However, certain procedure-related problems and unrealistic patient expectations may detract specialists from indicating DBS more widely despite significant clinical effects.
Methods: This review provides a pragmatic educational summary of the most conflicting postoperative management issues in patients undergoing DBS for PD.
Results: DBS in PD has been associated with certain complications and post-procedural management issues, which can complicate surgical outcome interpretation. Many PD patients consider DBS outcomes negative due to unfulfilled expectations, even when significant motor symptom improvement is achieved. Speech, gait, postural stability, and cognition may worsen after DBS and body weight may increase. Although DBS may induce impulse control disorders in some cases, in others, it may actually improve them when dopamine agonist dosage is reduced after surgery. However, apathy may also arise, especially when dopaminergic medication tapering is rapid. Gradual loss of response with time suggests disease progression, rather than the wearing off of DBS effects. Furthermore, implantable pulse generator expiration is considered a movement disorder emergency, as it may worsen parkinsonian symptoms or cause life-threatening akinetic crises due to malignant DBS withdrawal syndrome.
Conclusion: Major unsolved issues occurring after DBS therapy preclude complete patient satisfaction. Multidisciplinary management at experienced centers, as well as careful and comprehensive delivery of information to patients, should contribute to make DBS outcome expectations more realistic and allow post procedural complications to be better accepted.

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or internal globus pallidus (GPi) is an effective, widely used treatment for Parkinson's disease (PD) and probably represents the most important treatment advance since the introduction of levodopa.[1–4] The Movement Disorder Society evidence-based review on PD motor symptom treatment reported DBS was efficacious for motor complications.[5] DBS effects are not fully understood, but are probably due to selective modulation of disrupted basal ganglia thalamocortical circuits and basal ganglia–brainstem projections, allowing more normal motor and non-motor network function.[6] The primary indication is for disabling PD motor complications, such as dyskinesias or motor fluctuations not well controlled or unresponsive to best available medical treatment.[7–10] Long-term results have demonstrated significant clinical PD improvement in cardinal dopaminergic-responsive motor and non-motor features, as well as in quality of life (QoL) and activities of daily living.[3,10–15] Individual patient outcomes depend on several factors, including target selection, electrode location, programming settings, appropriate medical management, age, expected benefit, and perhaps genotype, among others.[2,16]

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Patients with mild to moderate motor complications lasting less than two years may benefit as much from DBS in terms of QoL and motor outcomes, as patients with advanced PD.[9] However, ideal timing for surgery remains a matter of debate.[17]

Partial or incomplete response to DBS in PD patients may be, in part, due to inappropriate patient selection or suboptimal DBS electrode placement. However, even in well-selected cases with improvement of cardinal motor signs and symptoms after correct DBS targeting, results may still fall short of individual patient expectations, limiting more widespread application of the procedure.[17]

Highlighting the importance of such issues, a new DBS Impairment Scale (DBS-IS)[18] has been developed, measuring specific STN-DBS problems or impairments, which may cause symptoms to remain unchanged, worsen, or even to arise after DBS implantation.[19]

The aim of this pragmatic educational review directed to referring physicians and clinicians who follow PD patients after DBS surgery, is to address the more common postoperative and long-term follow-up issues observed during routine clinical practice. These include partial or incomplete PD symptom response resulting from procedure-related limitations, long-term complications, or disease progression. Early detection of these common challenges may help improve general PD patient management by clinicians.

Dealing with Patient's Unrealistic Expectations

PD patients who undergo DBS have specific hopes and expectations regarding surgical outcome that are not limited solely to motor function improvement.[20] In one study, out of 28 patients undergoing DBS-STN, 25% were disappointed with the outcome, 32% were indifferent, and only 43% perceived the result as positive.[21] Higher apathy, depression, and axial symptom scores prior to DBS were shown to predict negative subjective perception of outcome.[20,21] In addition, patients often overestimated daily activity function levels and underestimated present motor impairment prior to surgery, ultimately misinterpreting post procedural improvement magnitude.[22] Kubu and coworkers identified significant lack of correlation between symptom goal severity ratings and standard clinical research metrics.[23] Improvements in tremor, gait, non-motor symptoms, interpersonal relationships, work capacity, and vocational pursuits appeared more important to patients accepting to undergo DBS.[23] In line with this, a prospective study of 21 patients receiving STN-DBS found occupational function, interpersonal relationships, and leisure activities did not improve after surgery.[24] Patient expectations regarding professional life, activities of daily living, marital relations, and social adjustments were usually not appropriately met.[25–27]

Author's pragmatic recommendations: *Clinicians should identify individuals at risk of perceiving postoperative outcomes as unsatisfactory, and analyze realistic and unrealistic expectations of individual patients prior to DBS in greater detail.*[20,27] *Psychosocial adjustment after DBS may be improved by providing patients and caregivers with psychological support, administering specific medication, or modifying stimulation settings as well as by teaching strategies to overcome surgery-related stress—all key factors enhancing patient satisfaction levels.*[27]

Caregiver Burden After DBS

Consequences of surgery on caregivers have been explored in more detail in recent years. A cross-sectional retrospective study on 275 patients who had undergone DBS found that although DBS positive effects on QoL were significant compared to non-surgical patients, analysis of a multidimensional caregiver strain index found no differences in caregiver burden between groups.[28] Two other studies showed similar findings.[25,29] An analysis of 12 patients undergoing DBS for PD using the Caregiver Burden Inventory failed to uncover changes in caregiver burden six months after surgery, despite significant patient improvement in several motor and non-motor symptoms.[29] Another study of 25 patients and caregivers reported over half the caregivers rated their subjective well-being as negative after a one-year follow-up.[25]

Author's pragmatic recommendations: *Social adjustment consequences of STN-DBS are still a subject of debate as no specific factor linked to postoperative maladjustment has been identified. However, mismatch between real and imagined expectations of both patients and caregivers may play an important role.*[30] *Before surgery, physicians should help families better understand potential changes in family roles and attempt to alleviate stress surrounding the perioperative period.*[27] *Psychoeducational interventions accompanying medical treatments have shown positive impact on both patient and caregiver emotional adjustment,*[31] *although such interventions have only recently been explored in a single study in PD patients following DBS.*[32]

Unsolved Motor and Non-motor Issues

Speech Disturbances

Speech disorders (intelligibility, pitch variation, worsening hypophonia, stuttering, and speech articulation problems) are common adverse effects in PD patients treated with STN-DBS.[13,33–36] Speech disturbances may occur due to a combination of DBS effects and disease progression, as is also the case for gait disorders developing after surgery.[13,37] Predictive factors for speech intelligibility after DBS include less preoperative clarity, presence of speech disturbances while taking ON-medication, longer disease duration, higher frequency or increased amplitude of stimulation, and more medial and/or posterior STN placement.[31,38–41] In clinical practice, trying with low frequency stimulation appears to be beneficial even in advanced PD.[42] Also, offering patients the Lee Silverman Voice Treatment, an intensive speech training program, may benefit patients with speech disturbances after STN-DBS, as suggested by a study.[43] However, a second study found variable results, suggesting the need for additional investigation.[44]

Stuttering may develop after surgery or worsen if already present.[45] Speech fluency may improve when DBS is off, suggesting a direct effect of stimulation.[45] However, results of a cross-sectional

study on 76 PD patients with STN-DBS versus 33 patients treated medically found that although stuttering worsened after STN-DBS, this was mainly due to aging and PD itself.[36] Family history of stuttering was found to be an important risk factor for developing the disorder after STN-DBS, suggesting a possible genetic cause.[46]

Author's pragmatic recommendations: *Physicians should be aware and advise patients that speech disorders are common after STN-DBS. Should these occur, low frequency stimulation and/or intensive speech training program can be offered to help mitigate this adverse effect.*

Freezing of Gait and Balance Impairment

PD patients with marked freezing of gait (FoG) unresponsive to levodopa or elevated postural instability and gait disorder (PIGD) scores are less favorable candidates for DBS than patients experiencing relief of such symptoms during the "on" state.[47] Unlike effects of DBS on cardinal PD motor features, benefits on axial symptoms, in particular PIGD, are less consistent.[1,3,13,48] A meta-analysis of long-term effects of DBS on PIGD revealed that, irrespective of the target selected, DBS did not improve PIGD features to the same degree as cardinal motor symptoms, and that GPi-DBS might preserve gait and posture better than STN-DBS.[49] Symptom worsening following DBS is likely to be multifactorial, and may be due to cognitive decline, disease progression, electrode location, or actually be induced by the stimulation per se.[12,50,51]

Author's pragmatic recommendations: *FoG developing or persisting immediately after DBS can be treated by either avoiding abrupt dopaminergic medication decrease, or increasing stimulation amplitude.*[52] *Adding methylphenidate and amantadine after DBS surgery may also improve FoG.*[53,54] FOG *development after long-term DBS therapy may be due to disease progression. Low frequency (60–80 Hz) stimulation has been recommended for FoG or PIGD unresponsive to several years of high frequency DBS stimulation.*[55,56] *However, improvements are not always immediate, or sustained.*[57,58]

Postural Disorders

DBS effects on postural control are ambiguous. Numerous case reports show slight to considerable benefit on camptocormia during the first six months after DBS, often lasting over two years.[59–64] Mean thoraco-lumbar angle decrease after STN-DBS was between 78% and 89%.[62–64] However, other reports have not shown camptocormia improvement.[59,61,65] In addition, DBS did not prevent camptocormic posture development.[61,66] In a large observational cohort of 25 PD patients with camptocormia treated with bilateral STN-DBS, duration of camptocormia of less than 1.5 years prior to DBS treatment was the most relevant prognostic factor of positive outcome.[62] Bending angle magnitude, motor severity, dopaminergic treatment, PD duration showed no influence, nor did age or gender.[62] Although PD camptocormia pathophysiology and DBS effects are poorly understood, amelioration may be due either to improvement in paraspinal muscles dystonia and rigidity[59,64] or to restoration of proprioceptive function.[62] Pisa syndrome has been described as a complication of unilateral subthalomotomy or pallidotomy.[67,68] However, mild to moderate Pisa syndrome improvement has also been reported after bilateral STN-DBS.[59]

Author's pragmatic recommendations: *Postural disorder treatment using DBS might be of benefit when performed at early stages of the development of this motor feature. There is no current evidence to support postural disorders as principal or single indication for DBS.*

Behavioral and Cognitive Issues After DBS

Neuropsychiatric symptoms arising after the procedure are mainly transient and treatable.[69–71] Correct electrode trajectory and placement are crucial factors to avoid these adverse events.[72] No major differences have been observed in behavioral outcomes between patients receiving GPi-DBS versus STN-DBS.[73]

Apathy

Apathy has been repeatedly reported as a possible adverse effect of STN-DBS, however literature on the topic is controversial.[74–77] Drapier and colleagues found significant worsening of apathy scores three to six months after surgery.[74] Another study of 88 patients found apathy was present in 27% one year after STN-DBS, with reduced QoL scores compared to patients without apathy.[76] Preoperative dyskinesia severity, non-motor fluctuations during regular daily life activities, and anxiety scores during the baseline levodopa challenge have been proposed as independent predictors of postoperative apathy.[75,77] Apathy might also be caused by rapid and aggressive dopaminergic drug reduction or withdrawal as stated by a prospectively cohort of 63 patients receiving STN-DBS, in which mean reduction in dopaminergic treatment was 73%.[78] In another study conducted by the same authors, apathy occurred on average 4 months after surgery and after drastic dopaminergic treatment reduction in 54% of patients, but was reversible in half, after dopamine agonist restitution, by 12-months follow-up.[77] In contrast to the abovementioned studies, an observational study in 19 patients undergoing STN-DBS found no changes in apathy scores with improvement in mood.[79] A more recent study also failed to find significant differences in apathy prevalence or severity between STN-DBS treated patients or those receiving pharmacological treatment alone.[80]

Author's pragmatic recommendations: *Currently, no specific pharmacological treatment has been described for apathy developing after DBS. Careful medication reduction is recommended to prevent postoperative apathy. If medication reduction is necessary, increasing intervals between medication dosages or sequential discontinuation of amantadine, catechol-O-methyltransferase, or monoamine oxidase inhibitors should be attempted first.*[69,81] *Slow decrease of levodopa or dopamine agonist dosage should follow.*

Anxiety

Anxiety disorders in PD are frequently comorbid with depression. Anxiety may improve after surgery but worsen long term.[82] A study comparing PD patients undergoing STN-DBS versus

patients on medication found only a short-term anxiety decrease associated with motor function improvement in those on medication;[83] however, this effect seemed to decrease with time and was later confirmed to be independent of study design or instruments used.[84]

Author's pragmatic recommendations: *Which clinical characteristics are significant amongst PD patients with anxiety? How does comorbid depression influence the likelihood of improving of worsening anxiety after DBS? These are both issues that should be urgently explored in randomized controlled trials. So far, no pharmacologic or non-pharmacologic interventions have proven effective, including cognitive behavioral therapy, to treat anxiety disorders in PD patients after DBS surgery.*

Depression

Immediately after DBS, patients manifest increased emotional reactivity; however, depression is rare.[21] Randomized multicentric studies showed improvement in depression after DBS in patients with PD.[85,86] However, higher prevalence of depression after STN-DBS was also found.[87]

Author's pragmatic recommendations: *Several antidepressants, including tricyclics (TCAs), selective serotonin reuptake inhibitors, and venlafaxine are recommended for depression in PD, although these have not yet specifically been explored in PD patients developing depression after DBS. Decrement of dopamine drug dose could explain depression after DBS, which may be transient and responds well to dopaminergic therapy (especially dopamine agonists) and cognitive behavioral therapy.*[69] *Candidate selection is key to prevent depression.*[70]

Suicide

A higher than expected suicide rate has been reported repeatedly in PD patients after STN-DBS.[88,89] One retrospective analysis of over 5000 PD patients with STN-DBS showed dramatic increase in suicide rates in the first year after surgery,[89] and a retrospective survey on 200 patients showed 2% had attempted and 1% had actually committed suicide.[88] No clear predictors for suicidal behavior were found, although it was associated with postoperative depression and/or impulse control disorders (ICD).[88,89] In contrast to previous studies, a randomized controlled study comparing DBS (n = 121) to best medical treatment (n = 134) found no direct association between suicidal behavior and DBS.[90]

Author's pragmatic recommendations: *Candidate selection is key to avoid suicide ideation or attempts after STN-DBS. Clinicians should be aware and actively screen during follow-up visits for any indication of these disturbances after DBS.*

Impulse Control Disorders

The relationship between DBS and ICD is controversial.[91] Bilateral STN-DBS was found to negatively affect decision-making during acute postoperative stages, to improve decision-making under risk, or to be unaffected.[92–94] STN-DBS has been identified as an independent risk factor for binge eating,[95,96] to induce "punding," and worsen ICD.[97] Hypersexuality and hypomania were also associated with STN-DBS.[82,98,99] However, ICD may also resolve or improve after surgery.[78,91,95] Long-term follow-up of patients with STN-DBS showed pre surgery ICD was abolished in most patients and dopamine agonist use reduced,[95] as was dopamine dysregulation syndrome.[100] New onset ICD was rare and transient with the exception of compulsive eating.[95]

Author's pragmatic recommendations: *Selecting the STN as the electrode target, as well as reduction of medication after surgery are valid strategies to treat severe ICD.*[78,101] *If ICD develops after surgery, stimulation diffusion or direct stimulation of STN-related limbic circuits should be checked. If this is not the cause, dopamine agonist discontinuation or tapering, as well as psychiatric evaluation and use of quetiapine or clozapine are recommended.*

Cognition

Risk of cognitive decline might be higher after STN- than after GPi-DBS, as some comparative studies have indicated.[10,102,103] In contrast, other studies failed to find differences in cognitive impairment between either target.[4,73,104] Cognitive decline reported after DBS mainly affects frontal subcortical cognitive functions, such as verbal fluency, processing speed, attention, learning, and working memory.[73,105] Worse cognitive outcome after surgery remained unmodified regardless of DBS settings or "on" and "off" motor states, suggesting the cause might be related to lead trajectory or location.[70] Predictive factors for cognitive decline after DBS have not been explored in detail, with age and mild cognitive impairment prior to surgery yielding inconclusive results.[85,106]

Author's pragmatic recommendations: *Because more significant cognitive changes may occur after STN-DBS compared to GPi-DBS, target selection should be tailored to individual patient cognitive status. If cognitive or behavioral issues are a concern, GPi-DBS might be a better choice. Nevertheless, clinically relevant cognitive deterioration should not be expected after DBS. Ultimately, mild cognitive impairment or dementia after long-term DBS may be attributable to disease progression rather than to DBS surgery per se.*

Weight Gain

Although PD patients often lose weight, body mass index increase following DBS has been largely recognized as an adverse event.[107,108] It usually occurs during the first year after surgery[109,110] and may lead to overweight, obesity, or metabolic syndrome.[111] A prospective analysis with 16 months follow-up found most patients were overweight or obese at the expense of increased in fat mass.[109] Most studies found no correlation between postoperative weight gain and increased caloric intake, UPDRS motor scores, motor fluctuations, dopaminergic medication, depression, binge eating, dysphagia, olfactory function, age, or disease duration.[109–115] Some studies suggested that weight gain after surgery might occur due to reduced energy expenditure related to dyskinesias or tremor improvement.[110,113] Reduced resting and free-living energy expenditure and decreased lipid and protein oxidation after surgery, compared to levodopa-treated patients, may also cause weight gain.[114–117] Normalized metabolism after DBS-STN with unchanged intake favors weight

gain.[115] Comparison of targets found greater weight gain for GPi versus STN-DBS in two comparative studies (frequency 88% vs. 64% and degree 8.4% vs. 3.2%, respectively)[117,118] though two others did not.[112,119]

Author's pragmatic recommendations: *Individualized and structured nutritional interventions modulating dietary habits and physical activity may be effective for STN-DBS-induced weight gain.*[120] *Nutritional counseling prior to surgery may also help prevent weight gain after the procedure.*

Discriminating Between Disease Progression and DBS Response Decline

Long-term follow-up studies of DBS show motor response was sustained, as was reduction in dyskinesia and dopaminergic medication, to the point that classic motor manifestations may no longer be a major concern.[11,13,15,105,121] However, worsening of neuropsychiatric and axial features may reflect natural PD progression.[13,85] Gradual aggravation of less responsive or unresponsive motor or non-motor features with sustained cardinal motor feature improvement may reflect disease progression rather than wearing-off of DBS effects.[8,10,14,121] Conversely, apparent failure or tolerance to long-term GPi-DBS can be corrected or rescued by STN-DBS and vice versa, arguing in favor of DBS wearing off in isolated cases.[122,123] Nevertheless, whether decline is related to disease progression or reduction in DBS efficacy remains to be demonstrated in long-term studies including control groups.[124,125]

Author's pragmatic recommendations: *Current evidence has failed to support a neuroprotective effect of DBS for advanced PD symptoms. Cognitive decline, loss of postural reflexes, or freezing of gait may develop during long-term follow up regardless of persistent and sustained control of basic PD motor symptoms like tremor, rigidity, bradykinesia, and drug-induced dyskinesia. This remains one of the most challenging issues for patients and clinicians and should be carefully discussed with them and their families before surgery.*

Concerns with Battery End of Life

Implantable pulse generator (IPG) expiration can be considered a movement disorder emergency.[126] Battery cessation, accidental turn off, or removal of infected IPGs rapidly worsen parkinsonian symptoms,[126,127] and may cause life-threatening akinetic crises due to malignant DBS-withdrawal syndrome.[127–129] Patients with early onset, longstanding and advanced disease may be more prone to these effects.[127,129] Increasing dopaminergic medication is often ineffective.[127–129] Chronic DBS treatment must be urgently restored.[126,128,129] GPi-DBS may be safer in these situations as dopaminergic medication usually remains stable in contrast to considerable dose reduction after STN-DBS.[129] Major determinants of a short IPG battery lifespan include elevated energy consumption (high intensity or broader pulse width), charge density, and double monopolar or interleaving modes.[130–133] High intensity and long pulse width are often required in GPi-DBS due to larger GPi volume, associated to shorter IPG longevity.[133] Low-frequency stimulation and bipolar stimulation configuration as well as use of rechargeable devices help batteries last longer,[130,134] reducing costs and morbidity linked to replacements.[135]

Author's pragmatic recommendations: *Early replacement is recommended when low-battery or end-of-life signaling is detected. Replacement delays must be minimized to avoid fatal battery drain complications. If immediate IPG replacement is not possible, alternatives such as use of levodopa/carbidopa intestinal gel or apomorphine infusion therapy may be valid rescue options.*[127,136] *Radiofrequency lesion techniques, like pallidotomy or subthalamotomy, have been shown to be effective and safe and might be valid and inexpensive options for advanced cases when consistent and timely IPG replacement is unavailable, including countries with limited healthcare budgets.*[5,137–140]

DBS Complications and Hardware Malfunction

Hardware-related complications may occur during implantation, perioperatively, or during long-term follow up. In order of frequency and severity, hardware-related complications include infections, skin erosion, lead or extension fracture, lead tract fibrosis, electrode or IPG migration, and external interference with other devices.[138,141–143] Overall rates range between 4% to 20%,[141,142] depending on surgical team experience, patient idiosyncrasies, or manufacturer problems, adding significant morbidity, increasing costs from hospitalization, surgical revision, and antibiotic use.[142] Implanted hardware infections rates average 4.5%, ranging between 0 and 15% and depend on the definition applied.[1–4,141,144,145] They can occur any time after surgery, especially after repeated IPG replacements due to battery drain[144]. Intracerebral abscesses are rare, but potentially devastating if not diagnosed and treated early.[146] Skin complications like abrasions, ulcerations, aseptic necrosis, or hardware-related scalp erosion are not uncommon, ranging between 1% and 25%.[147–149]

Exceptional complications have been reported, like twiddler syndrome, in which spontaneous or intentional rotation of implantable cables or IPG resulting from external manipulation, dislodges leads, ultimately requiring surgical revision.[150] Twiddler syndrome risk might be reduced with non-absorbable sutures and dual anchor IPG caps.[150] Other rare complications include development of structural lesions around implanted DBS leads such as large aseptic cysts, which usually resolve after lead removal,[151] and non-infectious peri electrode edema that may produce disorientation, gait instability, headache, seizure, or acute confusion.[152]

Author's pragmatic recommendations: *Early recognition of hardware-related complications is important, but also difficult, as sometimes the only indications are progressive loss of DBS effects on symptoms. Management varies, in general however, if infection is localized, the intracranial component may be spared, and local and intravenous treatment performed with or without IPG extraction. When infections involve brain tissue or leads, the entire hardware should be removed and intravenous antibiotics given.*[153] *A 1.5 tesla MRI scan to rule out brain infection may be used for most DBS-IPG implants.*[154] *However, application should be*

analyzed on a case-by-case basis, as many different MRI scanners and scanning conditions are employed.

Concluding Remarks, Unmet Needs, and Future Directions

DBS is an excellent therapeutic option for disabling PD motor complications not controlled with medication. Complications rates are low in experienced centers, and long-term follow-up studies show therapeutic benefits last over 10 years. It substantially improves QoL, globally changing patients' lives, although it is not entirely exempt from "new" social and labor-related issues. However, certain motor and non-motor symptoms may not improve (or could worsen) after DBS, even in patients originally considered optimal candidates. This, in turn, causes dissatisfaction and requires complex postoperative management. Additionally, battery depletion and hardware-related complications are mostly unforeseeable and considered a medical emergency, causing life-threatening complications. Thirty years of successful implementation of DBS, applying perfect candidate selection, and with careful follow-up by highly experienced medical teams is not enough to eliminate potential negative outcomes. Technique, hardware issues, and currently used targets appear as the main limitations to further advances and sustained clinical improvement. Emerging technologies, such as automated closed-loop adaptive DBS, multiple-source stimulation, and directional current steering systems may improve DBS efficacy, minimizing adverse effects and device-related complications. Meanwhile, patients must be carefully and comprehensively informed of DBS limitations as well about alternative therapies, such as continuous infusion techniques, in order to dampen unrealistic expectations regarding results.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

MR: 1A, 1B, 1C, 3A, 3B
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