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Insulin Therapy

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Normal circulating plasma glucose concentration is maintained by a delicate constant balance between glucose utilization (i.e., glycolysis or storage as glycogen by various tissues) on one hand and glucose production on the other (i.e., glycogenolysis and gluconeogenesis induced in certain tissues, such as liver, muscle, renal parenchyma, and adipose tissue). During the late post-absorptive period or starvation, normal glucose concentration is maintained by facilitating glucose production while inhibiting glucose uptake. In contrast, during the immediate post-absorptive period, glucose is provided by conversion of dietary nutrients, i.e., complex carbohydrates as well as proteins and fats, with minor contribution by the hepatic glucose production.

Glucose is the major and most efficient fuel for maintenance of normal function by all cells in the body, and insulin is required for glucose entry and utilization in all these cells, with the only exceptions being the nervous system, the renal medulla, and erythrocytes. Alternatively, glucose production is promoted by counter-regulatory hormones, i.e,. glucagon, catecholamines, glucocorticoids, and human growth hormone in concert with declining insulin concentration.[1] Thus, in principle, the basic pathophysiology in development of hyperglycemia in diabetes involves increased glucose production and decreased glucose uptake by the tissues. In Type 1 diabetes mellitus, hyperglycemia results from lack of insulin secondary to destruction of pancreatic beta cells, while insulin resistance in concert with an altered insulin secretory pattern leads to hyperglycemia in Type 2 diabetes mellitus.[2]

Appropriate management of hyperglycemia in Type 1 diabetes requires exogenous insulin administration with attainment of a normal or near normal daily insulin secretary pattern in conformity with daily routine schedule of meals and activities. In Type 2 diabetes, the ideal therapy may include both the amelioration of the insulin resistance and improvement in insulin secretory pattern. Therefore, the knowledge of insulin pharmacokinetics is essential in physiolog-

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ic management of hyperglycemia in both Type 1 and Type 2 diabetes mellitus.

Insulin Pharmacokinetics

Pharmacokinetics is distinctly different for endogenously secreted insulin in comparison to exogenously administered insulin.[3] Normally, insulin is secreted by pancreatic beta cells directly into portal circulation and, therefore, is promptly utilized, cleared, and degraded by the liver (50%). The remaining amount then enters the systemic circulation and is utilized by other tissues (muscle, renal parenchyma, etc.) and therefore a little is excreted by the kidneys. The fate of exogenously administered insulin follows a distinctly different pattern. Initially, it enters the peripheral venous circulation and then is transported to all the tissues, including the liver and kidneys, via systemic arterial circulation. Therefore, the clearance of exogenously administered insulin occurs primarily by the kidneys. The exact pharmacokinetics of exogenously administered insulin also is influenced by several factors, including the type of insulin (*See Table 1*), the routes of administration (*See Table 2*), dose and site of administration, the rate of absorption, and the integrity of systemic circulation.[4] The circulating half-life following intravenous administration is extremely short (5-10 minutes) in comparison to other routes, although it is similar for both regular insulin and glargine insulin.[5] The larger the dose, the longer the half-life is, in conformity with exogenous administration of other drugs. However, the initiation, peak, and duration of action of insulin analogs also vary widely on subcutaneous administration. (*See Table 1.*)

Several factors influence the absorption of insulin following subcutaneous administration.[6,7] The rate of insulin absorption is inversely proportional to the concentration and volume of injected insulin. Insulin absorption is enhanced by a relatively increased subcutaneous blood flow (i.e., from exercise, massage, heat, etc.) or dilute insulin solution. In contrast, factors inducing decreased insulin absorption include compromised subcutaneous blood flow (i.e., from cold, shock, or standing), lipohypertrophy or atrophy at the site of subcutaneous administration, or occasionally local destruction by an antibody.[8] The absorption also is altered if insulin is administered via an erroneous route directly into the capillary or by the intramuscular instead of subcutaneous route. Finally, the rate of absorption varies with the site of administration for all insulins with the exception of insulin glargine.

The most rapid absorption occurs following subcutaneous administration into the abdominal wall, whereas the absorption is slowest for subcutaneous administration into the thighs, with subcutaneous administration into the arms leading to an intermediate rate.[9] In contrast, the rate of absorption of insulin glargine is almost identical irrespective of the site of subcutaneous administration.[10] Although the subcutaneous route is used most commonly, other routes are used in special circumstances. Intravenous insulin infusion is a preferred route in sick subjects during hospitalizations for diabetic ketoacidosis, hyperglycemic hyperosmolar state, or other acute illnesses (i.e., MI, stroke, sepsis, etc.) as well as during perioperative or perinatal periods.[11,12] Intraperitoneal administration has been used in subjects undergoing intermittent peritoneal dialysis or in a rare occurrence of destruction of insulin at the site of administration into subcutaneous tissue.[13-15] Alternatively, the intramuscular route has been used occasionally.[15]

Principles of Insulin Therapy

Desirable glycemic control [HbA1c < 7.0%] is shown to reduce, delay, or prevent the onset or progress of complications, as seen in the Diabetes Control Complications Trial (DCCT) as well in other studies.[16-21] The daily glycemic goals to achieve desirable HbA1c concentration consist of pre-meal blood sugar between 80-120 mg/dL and 2 hours post-meal blood glucose concentration of less than 140 mg/dL. The most effective tactic to achieve desirable diurnal glycemia in Type 1 diabetes mellitus is to mimic the normal insulin secretory pattern consisting of a constant basal insulin level without a peak between meals, with its longest duration between bedtime and breakfast the next day, and a bolus insulin expressed as a prompt rise within 15-30 minutes following each meal.

Therefore, what until recently was called intensive therapy now has become a standard of care. This strategy demands careful attention to lifestyle modifications used concurrently with attainment of a normal diurnal insulin pattern. Therefore, frequent adjustments of insulin dosage based on pre-meal and post-meal blood glucose concentrations may be required to meet the changing circumstances. Two approaches in this regard include: 1) multiple daily injections (MDI) of rapidly acting insulin administered as boluses prior to meals, with administration of either a single or a split dose of intermediate- or long-acting insulin to mimic the basal pattern; or 2) a continuous subcuta-

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Table 1. Pharmacology of Various Insulin Preparations

INSULIN	ONSET OF ACTION	PEAK ACTION	DURATION OF ACTION
NPH	1-2 hours	4-8 hours	12-18 hours
Lente	1-2 hours	4-8 hours	18-28 hours
Ultralente		4-8 hours	12-20 hours
Glargine	1 hour	None	20-24+ hours
Semi-lente	30-60 minutes	2-4 hours	5-8 hours
Regular	30-60 minutes	2-4 hours	5-8 hours
Lispro	5-15 minutes	1-2 hours	2-4 hours
Aspart	5-10 minutes	1-2 hours	2-4 hours

All the time periods are based on the first subcutaneous injection.

Table 2. Route of Insulin Administration

- Subcutaneous
- Intramuscular
- Intravenous
- Intraperitoneal
- Oral
- Rectal
- Nasal

neous insulin (CSII) administration along with pre-meal boluses of short-acting insulin.[16,19,22,23]

Ideal basal insulin should closely mimic normal pancreatic basal insulin secretion between meals with no distinct peak. The insulins used to achieve a basal effect until recently have been ultralente, lente, and NPH insulins. However, they fall short of achieving a basal pattern because of their profiles and, therefore, pose many disadvantages, including:

• Induction of a peak after administration that tends to cause an increase in the risk of nocturnal, fasting, and frequently daytime hypoglycemia;

• Variability in day-to-day profiles because of changing absorption following subcutaneous injection due to insoluble suspension in formulation;

• Less uniformity of peak levels depending on variability of absorption from various sites of administration;[8,9] and

• Because of the intermediate (18-24 hours) duration of action with lente or NPH insulins and even a longer duration with ultralente insulin, a single dose rarely is adequate to achieve consistent diurnal basal concentrations.

In contrast, insulin glargine tends to achieve a consistent level without a peak, close to a normal basal pattern lasting about 24 hours, with once-daily administration in most subjects.[24] However, attaining and maintaining a stable basal pattern is not adequate to control postprandial glycemia.

In normal individuals, plasma insulin levels peak within 30-60 minutes following meals and blunt early postprandial glycemic excursions. (*See Figure 1.*) In subjects with Type 1 diabetes mellitus, attempts therefore are made to mimic the postprandial insulin pattern by administering rapid-acting insulins (*see Table 1*) immediately prior to meals or occasionally immediately postmeal—especially in subjects with delayed gastric emptying due to gastroparesis as well as those with erratic eating patterns. Slower absorption from subcutaneous depots may result in a delay of the physiologic peak level after meals, with the induction of immediate postprandial (1-2 hours) hyperglycemia. Delayed absorption also may lead to inappropriately high levels of insulin between meals, leading to late postprandial (3-4 hours) hypoglycemia. Fortunately, the newer rapid-acting insulin analogs lispro, aspart, or glulisin appear to mimic more closely the kinetics of a postprandial physiologic endogenous insulin pattern and, therefore, in conjunction with insulin glargine, help achieve the overall daily physiologic insulin profile closer to the one noted in normal subjects.

Adults with Type 1 diabetes manifest only minimal or no insulin secretion. Therefore, their initial daily insulin requirements of 0.5-0.6 units per kilogram of body weight tend to be similar to an average daily insulin production in normal adults. The daily insulin requirement includes both the basal and the prandial needs. The basal requirement is approximately 40-60% of the total daily dose to maintain normal fasting as well as preprandial glycemia via inhibition of hepatic glucose output. The remainder of the daily dose is for pre-meal administration as rapid-acting insulin to blunt postprandial hyperglycemia. Subjects requiring fewer than 0.5 units per kilogram of body weight frequently demonstrate the presence of some endogenous insulin production. Alternatively, the lesser requirement at the initiation of insulin therapy in Type 1 diabetes mellitus may be due to increased insulin sensitivity because of the up-regulation of insulin receptors in the absence of insulin. Finally, the simultaneous presence of other disorders may lead to a reduced daily insulin requirement in subjects with both Type 1 and Type 2 diabetes mellitus. These other disorders include renal failure inducing decreased insulin clearance, a lack of the counter-regulatory hormones cortisol, thyroid hormones, and human growth hormone in the presence of adrenocortical insufficiency and hypothyroidism or hypopituitarism, respectively, and lack of catecholamines or inhibition of their effects in presence of autonomic dysfunction. The daily insulin requirement in children usually amounts to 0.1-0.2 units per kilogram of body weight and gradually rises to almost 1.0 unit per kilogram of body weight during adolescence before decreasing to adult levels, with the highest daily dose in adolescents being attributed to spurts of human growth hormone.

Basal insulin production also varies throughout the day because of the diurnal rhythm of counter-regulatory hormones (growth hormone and cortisol) as well as rises and falls in circulating catecholamine concentrations secondary to physical and emotional lability. This diurnal basal insulin pattern has become evident in subjects with Type 1 diabetes mellitus using an artificial endocrine pancreas (Biostator, closed loop system) and continuous subcutaneous insulin infusion or insulin pumps (CSII).

Figure 1. Physiologic Insulin Secretion

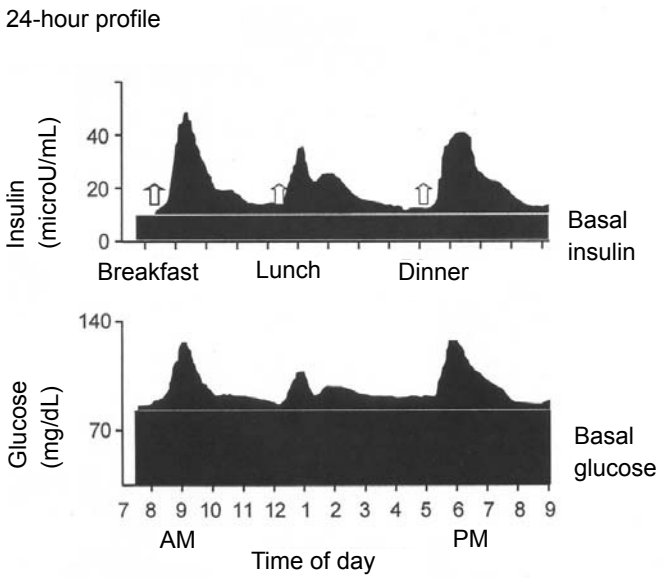


Table 3. Methods of Insulin Delivery

• Multiple daily dose injections of insulin as basal and pre-meal bolus, consisting of various mixtures of insulin preparations	Most readily available
• Continuous subcutaneous insulin infusion (CSII) using lispro or aspart	Insulin pump therapy—open loop system
• Artificial endocrine pancreas	Closed loop system
• Pancreas transplant	
• Islet cell transplant	

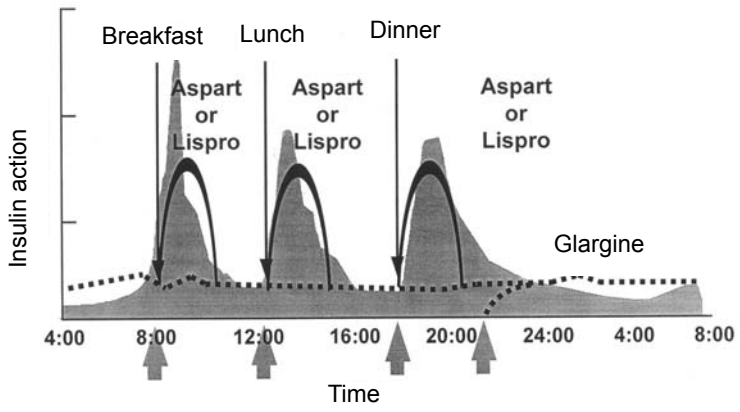
The basal insulin requirement of most subjects remains constant from 8 a.m. to midnight, with a decrease of almost 50% from midnight to 4 a.m., followed by an increase by about 50% from 4 a.m. to 8 a.m. once again attributable to a diurnal pattern of counter-regulatory hormones.[25-29]

Various insulin delivery methods for subcutaneous administration have evolved since the discovery of insulin. (*See Table 3.*) Historically, regular, or crystalline, insulin was the only formulation available and was administered subcutaneously pre-meal several times per day. Soon, the focus of therapy became convenience, and intermediate- or long-acting insulins were developed in an attempt to reduce daily multiple injections to one daily morning injection. The pitfalls of one daily injection in achieving control of glycemia were recognized with the advent of improved methods of assessment of diurnal glycemia, including home blood glucose monitoring. Therefore this regimen gave way to twice-daily injections of combinations of intermediate-acting and short-acting insulins, i.e., intensive conventional therapy of the 1970s. Although this regimen did improve glycemic control over the single dose regimen, the introduction of methodologies in assessment of long-term glycemic control over three months (i.e., HbA1c) or intermediate glycemic control over 2-3 weeks, with determination of fructosamine, and with further refinement in technological devices for capillary blood glucose determination, it became apparent that desirable glycemic control could not be attained or maintained with this intensive conventional therapy. With further advances in diabetes research, it also became apparent that pancreatic or islet cell transplantation or use of an artificial pancreas with computerized adjustment of the insulin infusion rate based on glucose readings obtained by a glucose sensor are the most effective methods in achieving near normal glycemia.[30,31] However, the transplantation of pancreas or islet cells has its own disadvantages, including the consequences of long-term immunosuppressive therapy and its side effects, the life span of the transplants themselves, and the need for recurrent transplants. Moreover, a portable closed loop system is yet to be developed.

With the use of a an artificial endocrine pancreas, the normal insulin secretory pattern in terms of basal and post-meal bursts was firmly established and the need for mimicking the normal physiologic insulin secretion to attain and maintain diurnal near normal glycemia was recognized, leading to the introduction of multiple (greater than 2) daily subcutaneous injections of basal and pre-meal short-acting insulins, i.e., true intensive therapy.

Finally, for achieving greater convenience over multiple injections, yet another method of optimal insulin delivery was developed in the form of continuous subcutaneous insulin infusion (insulin pump). However, present insulin pumps are open loop systems lacking glucose sensors and therefore need very close monitoring by an intelligent, mature, and committed patient who may need to perform capillary glucose testing several times per day, especially to avoid prolonged hyperglycemia or hypoglycemia. Hypoglycemia may be especially dreadful because it could remain sustained due to the pump's inability to discontinue or reduce the rate of insulin infusion, resulting in convulsion, coma, and occasionally death. In some patients, diabetic ketoacidosis occurs because of a lack of adequate frequency of blood glucose monitoring and declining appropriate assessment of equipment. This may occur from over-confidence and a lack-adaisical attitude on the part of patients, as well as their hesitancy to use subcutaneous insulin injections as instructed even in the presence of worsening hyperglycemia. Therefore, the insulin pumps need to be examined by personnel with the knowledge and experience of proper equipment functioning at least at a yearly interval. Moreover, it is important to monitor the patient's ability to maintain adequate technical performance. Therefore, insulin pumps must be reserved only for certain groups of patients, mainly those with Type 1 diabetes mellitus who are intent on continuing education and preparedness to perform frequent diurnal blood glucose monitoring and use subcutaneous insulin if needed in certain circumstances. Unfortunately, many patients do not belong to this category and, therefore, the brunt of insulin therapy revolves around a regimen consisting of multiple daily insulin injections

Figure 2. Basal/Bolus Treatment Program with Rapid- and Long-Acting Analogs



(MDI) consisting of a combination of basal and rapid-acting insulins. In actuality, several studies have demonstrated comparable efficacy of both MDI and CSII in achieving desirable glycemic goals.[32-34] Recently, NPH, lente, and ultralente insulins have given way to insulin glargine because of its profile in achieving a consistent physiologic basal insulin pattern. Therefore, subcutaneous administration of insulin glargine once or twice daily along with pre-meal rapid-acting bolus insulin appear to provide the most physiologic circulating insulin pattern throughout the day in most ambulatory patients consuming regular meals.

Initiation of Insulin Therapy in Type 1 Diabetes Mellitus

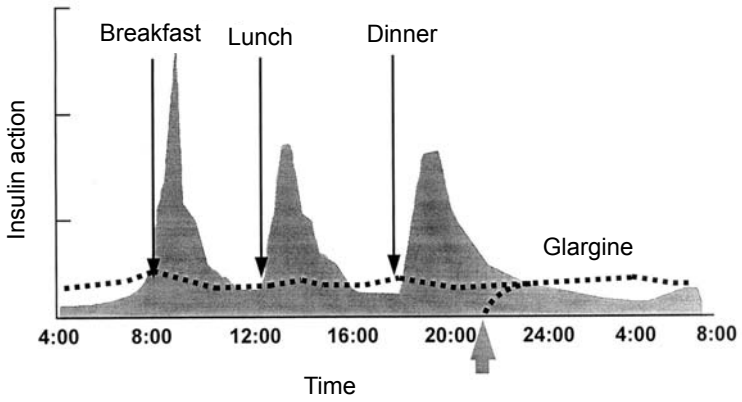
Conventional Regimen. Initially, a total daily dose is established as 0.4 units/kg of body weight and divided into two-thirds of intermediate and one-third of short-acting insulin, respectively. The dose of intermediate- and rapid-acting insulins is divided into two-thirds prior to breakfast and one-third prior to dinner. Individual doses then are adjusted based on blood sugar readings determined prior to meals or two hours after meals to attain the desirable levels of glycemia. Unfortunately, the adjustment of individual types in premixed forms, i.e., 70N/30 R, 75N/25 lispro, or 70 N/30 aspart, is not feasible. Therefore, this regimen in most patients, although simple, convenient, and acceptable, is unable to achieve desirable long-term glycemic control (HbA1C less than 7%) without frequent hypoglycemic episodes, especially during the night because of the peaks following the evening administration of intermediate-acting insulin.[35]

Another modification of this regimen involves use of intermediate-acting insulin at breakfast and bedtime with rapid-acting insulin prior to breakfast and dinner. This regimen may lower the incidence of nocturnal hypoglycemia and suppress the rise of blood glucose at dawn. However, in most patients this method also fails to attain and maintain a desirable glycemic target without significant reduction in episodes of hypoglycemia.[36] A small population of patients may be able to achieve adequate glycemic control as recommended by the American Diabetes Association (ADA) with one of these regimens and, therefore, could continue the same.

Intensive Conventional Regimen. This method intends to mimic the normal physiologic secretory pattern, consisting of several combinations of rapid-acting and intermediate- or long-acting insulins. One of these involves the administration of intermediate-acting insulin (NPH/lente) at bedtime with rapid-acting insulin lispro, aspart, or glulisin insulin prior to meals. Short-acting regular insulin may be used instead of the rapid-acting insulins because of its slightly longer duration of action anticipated to compensate for the lack of use of intermediate insulin during daytime, especially in the presence of gastroparesis. Another approach used for the intensive conventional regimen is the administration of long-acting insulin (ultralente) once or twice daily prior to breakfast and dinner mixed with either a short- or rapid-acting insulin, and yet another injection of short- or rapid-acting insulin prior to lunch. Another intensive regimen recently described consists of administering several injections (about 4), with mixtures of various insulins.

Finally, all these regimens require adjustments of short- or rapid-acting insulin dosages prior to meals based on the capillary blood glucose readings obtained prior to or at two hours after meals, i.e., supplemental or correction regimens. (*See Table 4.*) Although all these intensive regimens were able to attain and maintain desirable glycemic control (HbA1c less than 7%), the prevalence of hypoglycemia was three times greater in comparison to the conventional regimen,[16] a distinct obstacle in formulating a safe, effective, and viable option. The increased prevalence of hypoglycemia with these regimens was attributed to the peaks achieved by any of the insulins (ultralente, NPH, lente) used to mimic a normal basal pattern. These drawbacks were a major impetus for research leading to the synthesis of an ideal basal, peakless insulin glargine, which in combination with pre-meal rapid-acting insulin mimics normal physiologic insulin secretion. (*See Figures 1 and 2.*) Moreover, insulin glargine, because of several unique characteristics (*see Table 5*), opened a new era in research and development of other insulin analogs with similar properties. Several studies have established the efficacy of insulin glargine in achieving greater uniformity of glycemic control in comparison to NPH, lente, or ultralente insulin when used concurrently with the administration of rapid-acting insulin prior to meals, with a significant lowering of both the episodes of nocturnal hypoglycemia and rising rebound daytime glycemia.[37,38] Moreover, the dose of insulin glargine could be titrated to attain near normal morning fasting glycemia (90-130 mg/dL) because of fewer occurrences of nocturnal hypoglycemia, leading to the need for less rapid-acting insulin prior to meals with further decreased events of hypoglycemia during the daytime as well. Thus, overall use of insulin glargine instead of older intermediate-acting insulins for mimicking a normal basal pattern may attain and maintain HbA1c less than or equal to 7% as recommended by the ADA and even less than 6.5% as recommended recently by other organizations such as the American Association of Clinical Endocrinologists (AACE) and the International Diabetes Federation (IDF) without increasing significantly the risk of hypoglycemia. Finally, although the use of insulin glargine initially was approved for use at bedtime, newer studies have

Figure 3. Adding Basal Insulin to Oral Agents*: Insulin Glargine



*Must include a secretogogue to enhance postprandial insulin rise

demonstrated that it could be administered at any time during the day without loss of efficacy or greater risks of hypoglycemia as long as the time of administration remains the same every day.[39] This regimen may be more cost-effective than the older intensive regimens of the past. Cost savings may be realized because of reduction in nocturnal hypoglycemic events[40] due to its peakless profile, and during the day because of the decreased pre-meal dosage of rapid-acting insulin secondary to efficacy of glargine in achieving lower fasting blood sugar. Moreover, there is no need for a bedtime snack with blood sugars greater than or equal to 150 mg/dL because of reduced nocturnal hypoglycemia, and the better long-term glycemic control achievable by insulin glargine also may help lower both short-term and long-term costs. (*See Table 6.*) Finally, initiation of this regimen is simple and practical and can be achieved in all patients with Type 1 diabetes mellitus (*see Table 7*), including children and adolescents. However, mixing glargine (with acidic pH) with other insulins or normal saline that have neutral pH is not currently recommended because of a concern regarding alteration of their individual activity and efficacy. Therefore, glargine must not be mixed either in the syringe and or even at the site of subcutaneous administration. However, this recommendation may be more precautionary and presumptuous rather than factual, as noted in a recent report.[41]

Insulin Therapy in Type 2 Diabetes

The benefits of attaining and maintaining desirable glycemic control in lowering morbidity, mortality, and cost have been well-established.[16,17,19-21] Therefore, aggressive management of Type 2 diabetes with lifestyle modifications, oral hypoglycemic agents, and insulin to achieve recommended goals must become a standard medical practice. Moreover, in subjects with Type 2 diabetes, it is relatively easier to achieve more uniform glycemic control than in Type 1 diabetes, due to the influence of persistent, endogenous insulin secretion even during the late stage of disease.[42] Finally, subjects with Type 2 diabetes mellitus demonstrate better counter-regulatory mechanisms to combat hypoglycemia until the advanced stage of disease.[43] However, insulin therapy frequently is withheld or delayed in Type 2 diabetes mellitus because of the fear of hypoglycemia on the part of both the provider and the patient, and the fear of injection on the part of the patient. Another reason for withholding or delaying administration of insulin is the erroneous impression on the part of the provider that insulin is atherogenic in nature. This is a misconception and misrepresentation derived from epidemiological studies showing a relationship between hyperinsulinemia and cardiovascular outcomes.[45-47] One must realize that the adverse cardiovascular outcomes are secondary to insulin resistance, and hyperinsulinemia was a simple, calculable, mathematical surrogate marker of insulin resistance. In fact, several studies have shown that HbA1c levels are closely related to cardiovascular outcomes as well as other complications in Type 2 diabetes mellitus, and that intensive insulin therapy by achieving desirable glycemic control may delay the onset or retard the progress of these complications.[47-50] Recent studies have demonstrated improvement in outcomes with insulin therapy, lowering glycemic levels even in sick non-diabetic subjects via amelioration of inflammation, improvement in endothelial function, and enhancement of immune mechanism.[51-54] Therefore, the initiation of insulin in Type 2 diabetes must not be delayed or withheld in appropriate situations (*see Table 8*), since the lack of insulin use frequently leads to worsening manifestations with a delay in recovery and prolonged hospitalization.

Historically, in ambulatory subjects with a lapse of glycemic control while receiving oral agents, administration of NPH insulin at bedtime, 70/30, N/R insulin prior to supper, or ultralente insulin prior to breakfast were used in combination with oral agents (i.e., sulfonylurea) to provide basal insulin during the night to blunt nocturnal hepatic glucose production and lower fasting glycemia.[55-59] Simultaneously, these insulins also achieve early or late nocturnal peak, inhibit release of endogenous insulin, and therefore enhance insulin stores in beta cells. Administration of sulfonylurea enhances release of this stored insulin following a meal and blunts post-prandial glycemia during the daytime. Sulfonylureas, especially glimepiride, also may improve sensitivity of tissues to exogenous insulin and lower glycemia by enhancing glucose uptake.[60-62] Alternatively, insulin sensitizers (i.e., metformin and glitazone) blunt diurnal glycemia by enhancing insulin sensitivity in the peripheral tissues to exogenous insulin. Therefore it was anticipated that use of insulin sensitizers may lower the daily insulin dose more than sulfonylurea. However, exactly the opposite finding was noted in studies, which demonstrated greater lowering of the daily insulin dose by sulfonylurea in comparison to either metformin or the presently approved glitazones.[63-65] Also, using a combination of sulfonylurea with metformin appears to lower the daily insulin dose maximally, with a greater reduction in hypoglycemic events as well as weight gain.[66] Other benefits may be gained by such a combination therapy with insulin in comparison to insulin monotherapy. One injection of insulin frequently used in a com-

Table 4. Correction Dose of Rapid-Acting Insulin Based on Pre-meal Blood Glucose

Target of 100-150 mg/dL

PRE-MEAL OR BEDTIME BLOOD GLUCOSE (MG/DL)	RAPID-ACTING INSULIN *
< 50	- 2 units
51-100	- 1 unit
101-150	No change
151-200	+ 1 unit
201-250	+ 2 units
251-300	+ 3 units
> 300	+ 4 units

*Adjustment can be made based on insulin sensitivity in individual patient.
*Additional adjustment can also be made for ketones.

Table 5. Properties of Glargine Insulin

- Long-lasting, around 24 hours effect
- Convenience of once-daily administration
- Smooth, almost peakless profile
- Reproducible and predictable profile with low intra-subject variability from day to day
- No clinical differences in action when administered at different injection sites
- Reduced risk of nocturnal hypoglycemia

Table 6. Initiation of Glargine Insulin in Type 1 DM

- New onset—Total daily dose of insulin 0.4 units/kg body weight
  Insulin glargine 40-60%; Rapid-acting insulin 60-40%
- Conversion from ultralente or NPH: Reduce 20% dose
- Use only 50% of calculated dose first time if patient has taken prior shot, full dose with next dose
- Adjust dose by 4 units every 3-7 days to achieve a fasting glucose of 120 mg/dL
- Adjust dose every 3-7 days to achieve a fasting glucose of 80-120 mg/dL
- Adjust rapid-acting insulin based on pre-meal and HS blood glucose

bination regimen in contrast to multiple injections required with insulin monotherapy to achieve reasonable glycemic control distinctly provides a greater convenience and therefore renders better compliance, especially in the elderly. Furthermore, the smaller amount of weight gain noted with the combination therapy in comparison to insulin monotherapy may be beneficial in preventing or delaying consequences of weight gain, particularly worsening insulin resistance with increasing daily insulin dose and worsening lipid profile.[67] Finally, combination therapy consisting of insulin and sulphonylurea also has been shown to be more cost-effective in comparison to insulin monotherapy.[68]

With all of these different regimens, however, using older intermediate- or long-acting insulins to attain and maintain HbA1C less than or equal to 7.0% was difficult because of a significant prevalence of nocturnal hypoglycemia necessitating a decrease of the insulin dose. Recent studies using insulin glargine with a more physiological basal profile have demonstrated that a significantly greater number of subjects using insulin glargine at bedtime attained HbA1C less than or equal to 7.0% with fewer hypoglycemic events in comparison to administration of NPH insulin at the same time.[69,70] Furthermore, insulin glargine may be administered at any time of the day (i.e., before breakfast, before lunch, or before dinner, or at bedtime) as long as the time remains the same every day without a lapse of glycemic control based on recent studies.[39,83] Thus basal insulin therapy may be initiated appropriately with insulin glargine in subjects with Type 2 diabetes mellitus who have lapsed adequate glycemic control on oral agents with adherence rate of more than 90%. (*See Table 9.*) However, a combination of oral agents with basal insulin must include a sulfonylurea, preferably glimepiride, because of its efficacy in facilitating both phases of postprandial insulin secretion to successfully ameliorate postprandial hyperglycemia.[84] (*See Figure 3.*) In the absence of sulfonylurea, sensitizers, especially glitazones, fail to improve postprandial insulin secretion necessitating preprandial administration of rapid-acting insulin.[85-87] The addition of rapid-acting insulin may not be necessary in some subjects with well-preserved endogenous insulin stores and production.

However, rapid-acting insulin may be used prior to meals if HbA1c remains greater than 6.5% despite achieving desirable fasting glycemia (80-120 mg/dL), suggesting persistent postprandial hyperglycemia confirmed by blood sugar readings.

Insulin in Diabetics Under Special Circumstances

Renal Failure. In patients with advanced nephropathy (creatinine clearance less than 20 mL/minute), the insulin requirement may be reduced by as much as 50%. Sometimes, patients with Type 2 diabetes mellitus who progress to advanced nephropathy discontinue insulin therapy as their residual insulin production in the presence of renal failure is sufficient to achieve desirable glycemic control. Institution of dialysis often leads to an increase in insulin requirement on the day of dialysis because of increased clearance, while remaining the same on days between dialysis sessions. In patients being managed with intermittent peritoneal dialysis, insulin can be administered intraperitoneally in a substantially larger dosage in comparison to the subcutaneous requirement.[13-15]

Pregnancy. Insulin is the only available modality of therapy even in Type 2 diabetes mellitus since oral agents are not approved for use in pregnancy.[71] The insulin analogs presently approved for usage during pregnancy are NPH, regular, and lispro insulin. Safety for other insulins, including glargine, has not been established. It may be a safe and efficacious option as described in an isolated case report;[72] however, routine use of insulin glargine must await further assessment. Insulin requirements may fall slightly during the first trimester, gradually followed by a rise in

Table 7. Probable Cost Advantages for Regimens Using Insulin Glargine

	GLARGINE	NPH OR ULTRALENTE	COST
Number of injections	4	3	L>N or U
Dose of rapid-acting insulin	Less because a.m. blood glucose of 80-110 mg/dL is achievable	Because a.m. blood glucose 80-110 mg/dL is less achievable due to increased nocturnal hypoglycemia	L<N or U
Bedtime snack	Only if bedtime blood glucose < 120 mg/dL	Always	L<N or U
Hypoglycemia	Less	More	L<N or U
Food intake/ weight gain	Less	More	L<N or U
Glycemic control	Better	Good	L<N or U

the second trimester, and reaching a peak in the third trimester. Immediately after delivery, however, the requirements decline precipitously and return to the pre-pregnancy dosage.[73-75] These patients need intense glycemic control and frequently need multiple daily injections of insulin or continuous subcutaneous insulin infusion along with close monitoring of blood sugars pre- and post-meals, at bedtime, and occasionally at 2 a.m.

Old Age. Adjustment of the insulin regimen at regular follow-up visits is essential because of declining renal function and a special need to avoid hypoglycemia, which could result in morbidity (i.e., stroke, MI, or occasionally even death). Administration of premixed insulin preparations may be adequate because of lack of need for intensive control and a greater need for prevention of hypoglycemia, therefore making it a convenient option and rendering better compliance.[76] In subjects with Type 2 diabetes mellitus, one injection of basal insulin in combination with oral agents often is adequate to attain a desirable glycemic goal with little risk of hypoglycemia. This therapy is more convenient and therefore results in better compliance in comparison to insulin monotherapy, frequently requiring multiple injections.

Children and Adolescents. Insulin was the only approved modality of treatment in this age group until recent approval of metformin for patients older than 10 years. Moreover, ongoing trials with other oral agents based on pathophysiology of the disorder offer a promise for treatment of Type 2 diabetes mellitus in these age groups. However, for present, insulin remains the only viable option in children younger than 10 years of age.

Table 8. Indications of Insulin Therapy in Type 2 Diabetes Mellitus

- Patients with lapse of glycemic control while receiving combinations of multiple medications in their maximum dosages
- Patients manifesting ketonuria, weight loss, and/or severe hyperglycemia, with symptoms especially at the time of diagnosis
- Intercurrent illness
- Pregnancy
- Major trauma or surgery
- Age younger than 10 years

Surgery. General anesthesia requires special precautions. The metabolic aim in a surgical patient is to avoid hypoglycemia and to prevent blood sugar excursions over 180 mg/dL. Elective surgery should be performed only after attaining desirable glycemic control. Generally, patients should receive the usual dose of insulin glargine on the day prior to surgery. Alternatively, in patients using older intermediate- or long-acting insulins (ultralente), 50% of the daily dose may be administered subcutaneously on the morning of surgery, with a reduction in the previous evening dose by 20%. During the day of surgery, an infusion of 5% dextrose at 100 mL per hour is advisable until resumption of oral intake, with subcutaneous administration of rapid-acting insulin every 3-4 hours to maintain blood sugar between 120-180 mg/dL. A more physiologic and effective option is IV insulin infusion at rate of 0.5-2 units per hour with hourly adjustment of the rate based on blood sugar readings, especially during procedures such as cardio-pulmonary bypass because of changing insulin requirements during hypothermia and re-warming stages. Finally, the pre-operative regimen should be resumed with initiation of oral intake.[77,78]

Diabetic Gastroparesis. Pre-meal administration of a short-acting insulin over a rapid-acting insulin may be more physiologic in these patients because of the delay in digestion and absorption of food causing erratic postprandial glucose levels. Alternatively, rapid-acting insulin also could be administered immediately after a meal with adjustment of the dose depending on the amount of intake.

Diabetic Ketoacidosis or Hyperosmolar Nonketotic Coma. Intravenous regular insulin administration is the most appropriate therapeutic option.[79] Initial bolus based on body weight and degree of hyperglycemia (0.1 unit/kg with blood sugar between 200-500 mg/dL, 0.15 units/kg with blood sugar between 500-1,000 mg/dL, and 0.2 unit/kg with blood sugar greater than 1000 mg/dL) is administered followed by a continuous IV infusion at a rate of 0.1 unit/kg/hour with re-administration of a bolus as well as adjustment of infusion rate to achieve a 10% fall in blood glucose at hourly intervals. The important contributions to therapy include a frequent and close follow-up assessment for adequate insulinization and maintenance of fluid and electrolyte balance.

For further details, readers are referred to ADA practice guidelines for 2004.[80]

Table 9. Initiation of Insulin Glargine in Type 2 Diabetes Mellitus

HBA1C	NUMBER OF ORAL AGENTS	INITIATING DOSE OF GLARGINE
> 8.0%	1	0.4 units/kg
> 8.0%	2	0.2 units/kg
7-8%	1	0.2 units/kg
7-8%	2	0.1 units/kg

- Conversion from ultralente or NPH: Reduce 20% dose
- Use only 50% of calculated dose first time if patient has taken prior shot, full dose with next dose
- Adjust dose by 4 units every 3-7 days to achieve a fasting glucose of 120 mg/dL
- Adjust dose every 3-7 days to achieve a fasting glucose of 80-120 mg/dL
- Adjust rapid-acting insulin based on pre-meal and HS blood glucose

Insulin Use in Subjects Without Diabetes Mellitus

Insulin had not been used in non-diabetic subjects because of fear of hypoglycemia. Initial use of insulin in subjects without diabetes was conducted in the NIH-sponsored Diabetes Prevention Protocol.[81] In this study, insulin was administered daily or intermittently to the pro-bands of subjects with Type 1 diabetes mellitus prior to onset of hyperglycemia or ketonemia during a pre-diabetes state in the presence of islet cell antibodies and a decline in first phase insulin secretion following IV glucose administration. The study was terminated because no significant benefit was noted in prevention of Type 1 diabetes mellitus. The authors have demonstrated effective use of insulin in reversing the catabolic state into anabolic process in subjects with AIDS.[82] In these studies, with improvement in nutritional status, several laboratory parameters normalized, and enhancement of immune mechanisms were noted. Similarly, intravenous insulin infusion lowered stress hyperglycemic levels of 160-200 mg/dL to 110-120 mg/dL and improved outcomes in critically ill subjects.[51] None of these studies documented significant symptomatic or asymptomatic hypoglycemia, allaying concerns about administration of insulin in non-diabetic subjects.

Side Effects of Insulin Therapy

The side effects of insulin therapy include the following:

Hypoglycemia. Fortunately, occurrence of hypoglycemia has declined over the years with the advent of newer insulins and better understanding of insulin pharmacokinetics.

Post-hypoglycemic Hyperglycemia (Somogyi Phenomenon). This has declined as well because of reduction in number of hypoglycemic events.

Lipoatrophy or Lipohypertrophy. Lipoatrophy is immune-mediated and less frequent now with the use of purified synthetic insulins.

Insulin Allergy. The occurrence of this side effect is greatly reduced with the use of purified forms of animal insulins and even more with the use of insulins synthesized by recombinant DNA technology.

Edema. This is a rare phenomenon due to the sodium-retaining effect of insulin on the kidney, with a minor contribution by declining natriuresis secondary to decreasing glucagon concentrations.

Summary

Attainment and maintenance of near normal diurnal glycemia with achieving HbA1c less than or equal to 7.0% or less than or equal to 6.5% in subjects with both Type 1 and Type 2 diabetes mellitus has been recommended by many organizations. However, the glycemic target must be individualized. In the young and middle-aged population, this goal is acceptable because of the persistence of hypoglycemia awareness and their ability to combat hypoglycemia without outside assistance. In contrast, the glycemic goal may be raised to avoid hypoglycemia as much as possible in the elderly or in patients with cardiovascular disease or hypoglycemia unawareness, since a hypoglycemic event could be prolonged and may induce a significant morbidity, i.e. stroke, myocardial infarction, and even mortality. Therefore, the appropriate glycemic target in an individual subject must be the lowest HbA1c achievable with minimal hypoglycemia in the presence of awareness or none at all, especially in the elderly.

Insulin administration is the only therapeutic option in subjects with Type 1 diabetes mellitus and is needed for survival. The best approach of insulin therapy in Type 1 diabetes mellitus involves provision of exogenous insulin analogs to mimic the normal endogenous insulin secretory pattern consisting of basal insulin between meals and prompt insulin bursts following meals. Historically, the attainment of this pattern has been difficult and unrealistic because none of the intermediate- or long-acting insulins provide basal peakless profiles. Moreover, the peaks often are erratic and cause significant occurrence of hypoglycemic events, especially during the night, thus preventing attainment of near normal glycemia and a desirable HbA1c level. With the advent of insulin glargine, via its more physiologic basal property, a more uniform diurnal glycemic control with a decline in hypoglycemic events has become feasible. Presently, one injection of insulin glargine and pre-meal administration of rapid-acting insulin has been shown to achieve comparable glycemic outcomes attained by continuous subcutaneous insulin infusion, also described as insulin pump. Therefore, this insulin regimen may be preferred over older regimens in Type 1 diabetes mellitus.

Insulin therapy also is distinctly indicated in subjects with Type 2 diabetes mellitus. Insulin administration frequently is initiated in subjects lacking glycemic control while receiving oral agents in their maximum daily dose. This approach is equally or even more effective than insulin monotherapy and provides several other benefits, i.e., fewer hypoglycemic events, less weight gain, lower cost with a greater convenience, and, therefore, a better compliance. However, during pregnancy and in children younger than 10 years even with Type 2 diabetes mellitus, the only approved therapy by Food and Drug Administration is insulin. Finally, insulin therapy must not be withheld in patients with Type 2 diabetes mellitus in the presence of stressful circumstances or severe symptomatic

hyperglycemia and ketoacidosis, both requiring prompt resolution.

Recently, insulin therapy is being extended to subjects without diabetes mellitus in certain stressful circumstances with improvement in outcomes. Therefore, administration of newer insulin analogs in appropriate doses and at appropriate times during the day have significantly lowered the prevalence of adverse effects, including severe hypoglycemia, rendering this therapy safe and effective in both types of diabetes mellitus as well as in the non-diabetic population during certain situations.

Appendix: In September, an FDA advisory panel recommended approval of an inhaled insulin preparation. The inhaled insulin may be used as a substitute in place of preprandial rapid-acting insulin. It can achieve appropriate serum levels like other subcutaneous rapid-acting insulins but in markedly higher dosage. It may cause a minor reduction in pulmonary function in the long term, and absorption may be affected by acute or chronic lung or respiratory disease and probably smoking.

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Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

Physician CME Questions

65. The normal physiologic insulin secretory patterns consist of:
    A. circulating basal insulin concentration.
    B. a first phase or early (15-30 min) postprandial insulin rise.
    C. a second phase or late (90-120 min) postprandial insulin rise.
    D. All of the above

66. Which of the following statements is true regarding an insulin pump?
    A. It is an "open loop" system involving continuous subcutaneous administration of insulin without a glucose sensor.
    B. It is a "closed loop" system with ability to adjust the rate of subcutaneous administered insulin in response to circulating glucose concentration indicated by a glucose sensor of the system.
    C. It does not require preprandial insulin bolus administration.
    D. All of the above

67. Subcutaneous insulin glargine:
    A. must be administered at bedtime in all patients.
    B. may be administered at any time of day as long as the time remains about the same every day in most patients.
    C. must be administered in the morning before breakfast in all patients.
    D. may be administered at any time of day.

68. Insulin glargine must *not* be mixed with rapid-acting insulins because:
    A. they are synthesized by different technological processes.
    B. they are synthesized at different temperatures.
    C. they are synthesized as solutions with different individual pHs.
    D. they are synthesized from different animal sources.

69. Barriers to insulin therapy in subjects with Type 2 diabetes include:
    A. fear of injections on part of the patient.
    B. fear of hypoglycemia on part of both patient and provider.
    C. fear of increasing costs of treatment on part of both patient and provider.
    D. All of the above

CME Answer Key

65. D; 66. A; 67. B; 68. C; 69. D

In Future Issues: ***Common Arrhythmias***

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

The Use of Prophylactic Antibiotics for Neutropenia

Antibacterial prophylaxis is generally not recommended for neutropenic patients undergoing chemotherapy. Two studies in the Sept. 8 issue of the *New England Journal of Medicine* may change that recommendation. The first study from Italy looked at 760 adult patients who were undergoing treatment for acute leukemia, solid tumors, or lymphoma and were at risk for chemotherapy-induced neutropenia lasting more than 7 days. Many were undergoing stem cell transplantation. Patients were randomized received either oral levofloxacin 500 mg daily or placebo from the start of chemotherapy until the resolution of neutropenia. The rate of fever present for the duration of neutropenia was reduced in the levofloxacin group (65% levofloxacin prophylaxis, 85% placebo; RR, 0.76, 95% CI; $P = 0.001$). The levofloxacin group also had a lower rate of microbiologically documented infections (17% absolute difference in risk; $P < 0.001$), bacteremia (16% absolute difference in risk; $P < 0.001$), and single agent gram-negative bacteremias (7% absolute difference in risk; $P < 0.01$), compared to the placebo group. There was no difference in mortality, and there was no difference in outcomes between patients with acute leukemia or those with solid tumors or lymphoma. Treatment was generally well-tolerated. The authors conclude that prophylactic treatment with levofloxacin is an effective and well-tolerated way of preventing febrile episodes and other relevant infection-related outcomes in patients with cancer and profound and protracted neutropenia (Levofloxacin to Prevent Bacterial Infection in Patients with Cancer and Neutropenia. *N Engl J Med*. 2005;353:977-987).

The second study from England looked at 1565 patients undergoing cyclic chemotherapy for solid tumors or lymphoma who were at risk for temporary, severe neutropenia. Since these patients were receiving cyclic chemotherapy, the rate of neutropenia was significantly lower than the first study. Patients were randomized to receive levofloxacin 500 mg daily or placebo for 7 days during the expected neutropenia period. During the first cycle of chemotherapy, 3.5% of patients in the levofloxacin group had a least one febrile episode, compared with 7.9% in the placebo group ($P < 0.001$). During the entire chemotherapy course, 10.8% of patients in the levofloxacin group had a least one febrile episode, compared with 15.2% of patients in the placebo group ($P = 0$ .01); the rate of probable infection was 34.2% and 41.5%, respectively ($P = 0.004$). Hospitalization rates were significantly higher in the placebo group, and the rate of severe infection was twice as high in the placebo group (1.0% vs 2.0% [$P = 0$ .15]). The death rate was same in both groups. The authors concluded that prophylactic use of levofloxacin reduces the rate of fever, probable infection, and hospitalization (Cullen M, et al. Antibacterial Prophylaxis After Chemotherapy for

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Solid Tumors and Lymphomas. *N Engl J Med*. 2005;353:988-998).

An accompanying editorial suggests that these are important studies which provide more data on prophylactic antibiotics in neutropenia that had previously been available. However, further study still needs to define which patients are at highest risk and the period of greatest risk during chemotherapy. Most importantly, the emergence of resistant organisms, which was seen in the Italian study, is a major concern. The author states "If prophylactic antimicrobial therapy is to be adopted at a cancer center, it should be accompanied by vigorous infection-control practices and careful monitoring for the emergence of resistant organisms" (Baden LR. Prophylactic Antimicrobial Agents and the Importance of Fitness. *N Engl J Med*. 2005:353: 1052-1054).

Is It Hot In Here?

Hot flashes are common problem for women undergoing treatment for breast cancer. A new study suggests that gabapentin adjusted 900 mg per day may help alleviate symptoms. Four hundred twenty women, with breast cancer and 2 or more hot flashes per day, were randomly assigned to receive gabapentin 300 mg per day or gabapentin 900 mg/day or placebo in 3 divided doses for 8 weeks. The 900 mg per day does reduce hot flashes by 49% and 46% at 4 and 8 weeks, respectively. The 300 mg dose was not effective at a statistical level. The authors suggest that gabapentin 900 mg per day should be considered for treatment of hot flashes in women with breast cancer (Pandya KJ, et al. Gabapentin for Hot Flashes in 420 Women with Breast Cancer: A Randomised Double-Blind Placebo-Controlled Trial. *Lancet*. 2005;366:818-824).

Homeopathy vs Conventional Medicine

A new study suggests that homeopathy is no better than placebo in treating disease. Researchers from the University of Berne in Switzerland, reviewed over 100 clinical trials of homeopathy and conventional medicine. Eight large homeopathy trials were eventually used in a meta-analysis, along with 6 large conventional medicine trials. The odds ratio for homeopathy was 0.88 and for conventional medicine 0.58. When only the largest trials were used, the odds ratio for homeopathy was 0.96 and for conventional medicine 0.67. This suggests that the benefit from homeopathy is no better than random chance (Shang A, et al. Are the Clinical Effects of Homeopathy Placebo Effects? Comparative Study of Placebo-Controlled Trials of Homeopathy and Allopathy. *Lancet*. 2005; 366: 726-732). An accompanying editorial states "Now doctors need to be bold and honest with their patients about homeopathy's lack of benefit. . ." (The End of Homeopathy. *Lancet*. 2005;366:690). Homeopathy which uses very dilute solutions to treat disease has been popular in Europe; however, this study marks a trend away from homeopathy in England. The Swiss government also recently withdrew insurance coverage for homeopathy after a 5-year trial because it did not meet efficacy and cost effectiveness criteria.

FDA Actions

The FDA has approved a new 4-component vaccine for children aged 12 months to 12 years that includes measles, mumps, rubella, and varicella viruses. The approval was based on data showing effectiveness of the vaccine was similar to that of MMR (measles, mumps, and rubella) and varicella vaccine (Varivax). The new vaccine will be marketed under the trade name ProQuad by Merck & Co.

Sanofi-Synthelabo has received approval to market an extended release formulation of zolpidem (Ambien) for the treatment of insomnia. The new preparation is a bi-layered tablet that delivers the drug in 2 stages, a quick dissolving layer to induce sleep, and a slower release layer to provide sleep continuity. Ambien CR will be marketed in a 12.5 mg dose for adults and a 6.25 mg strength for patients 65 years and older.

The Senate has approved a bill to limit over-the-counter sales of pseudoephedrine, a key ingredient in the illicit manufacturing of methamphetamine. The bill which has bipartisan support, will require decongestant medications containing pseudoephedrine to be sold behind pharmacy counters and would limit how much any individual can buy to 7.5g a month (250 30 mg tablets).The bill also encourages a computer tracking system to limit multiple purchases at different stores and pharmacies. A similar bill is working its way to the House of Representatives.

The FDA is one step closer to approving Pfizer's inhaled insulin powder after an advisory panel voted 7-2 to urge approval. The preparation, which will be marketed under the trade name Exubera, is a short-acting insulin powder that is used before meals. The drug does not replace the need for long acting insulin injections. There have been concerns that Exubera may hamper lung function in diabetics, but Pfizer has been able to show 2-year data that suggest patients experience only minimal decrease in lung capacity that is reversible if the drug is stopped. ■